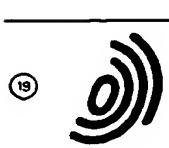


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Mishima-gun, Osaka(JP)

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Inventor: Takahashi; Kanji, c/o Ono

Pharmaceutical Co., Ltd.

Minase Res. Institute, 3-1-1 Sakurai

Shimamoto-cho

Mishima-gun, Osaka(JP)

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Inventor: Tokumoto, Hidekado, c/o Ono

Pharmaceutical Co. Ltd

Minase Res. Institute, 3-1-1 Sakurai

Shimamoto-cho

Mishima-gun, Osaka(JP)

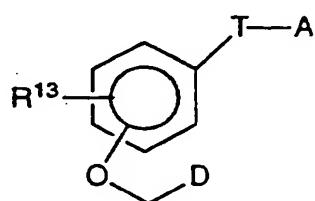
(33) Applicant: ONO PHARMACEUTICAL CO., LTD.  
1-5, Doshomachi 2-chome Chuo-ku  
Osaka-shi Osaka(JP)

(34) Inventor: Hamanaka, Nobuyuki, c/o Ono  
Pharmaceutical Co. Ltd  
Minase Res. Institute, 3-1-1 Sakurai  
Shimamoto-cho

(74) Representative: Henkel, Feller, Hänel &  
Partner  
Möhlstrasse 37  
D-81675 München (DE)

(54) Phenoxyacetic acid derivatives and pharmaceutical compositions containing them.

(55) We proposed a novel compound having an activity of PG<sub>I<sub>2</sub></sub> receptor agonist.  
A phenoxyacetic acid derivative of the formula



A is -C(R<sup>1</sup>)=N-OR<sup>2</sup>, -CH(R)NH-OR<sup>2</sup>, -COE, -SO<sub>2</sub>E, -CH<sub>2</sub>-NR<sup>3</sup>-Y, -Z-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>, -CH<sub>2</sub>-OR<sup>6</sup>, -CO<sub>2</sub>R<sup>6</sup>,  
-CH<sub>2</sub>-O-N=CR<sup>7</sup>R<sup>8</sup>, -CH<sub>2</sub>-O-NHCHR<sup>7</sup>R<sup>8</sup>, substituted by imidazolyl(methyl), pyrazolylmethyl, oxazolyl(methyl),  
thioxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolylmethyl;

T is alkylene, alkenylene, etc.;

D is -CO<sub>2</sub>R<sup>10</sup>, -CONR<sup>11</sup>R<sup>12</sup>;

E is (substitution) amino, hydrazino;

EP 0 558 062 A2

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EP 0 558 062 A2

Y is substituted (thio) carbonyl, substituted sulfonyl;

Z is -CH=N-, -CH<sub>2</sub>NR<sup>3</sup>-;

R<sup>1</sup>, R<sup>3</sup>, R<sup>10</sup>-R<sup>13</sup> is each H or alkyl, etc.;

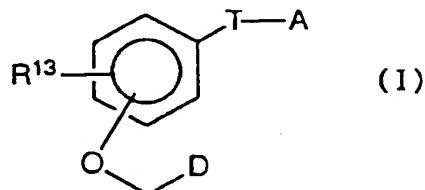
R<sup>2</sup>, R<sup>4</sup>-R<sup>9</sup> is each H, alkyl or alkyl substituted by phenyl or hetero ring, etc. and non-toxic salts thereof, non-toxic acid addition salts thereof, possess an agonistic on PG<sub>I2</sub> receptor, so it is useful for prevention and/or treatment of thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer and hypertension.

## Summary

This invention is related to phenoxyacetic acid derivatives.

More particularly, this invention is related to:

- 5 1) phenoxyacetic acid derivatives of the formula (I):



wherein all the symbols are the same meaning as hereafter defined, and non-toxic salts thereof and non-toxic acid addition salts thereof,

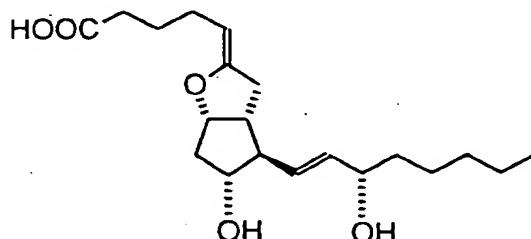
2) processes for the preparation thereof, and

- 20 3) pharmaceutical agents containing them as active ingredient.

## Background of the Invention

Prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) is a physiologically active natural substance having the following structural

- 25 formula, which is biosynthesized from Prostaglandin H<sub>2</sub> (PGH<sub>2</sub>) in the metabolic process in vivo called arachidonate cascade.



(see Nature, 263, 663(1976), Prostaglandins, 12, 685(1976), *ibid*, 12, 915(1976), *ibid*, 13, 375(1977) and Chemical and Engineering News, Dec. 20, 17(1976)).

PGI<sub>2</sub> has been confirmed to possess not only a very strong inhibitory activity on blood platelet aggregation but a dissociative activity on blood platelet aggregation, an inhibitory activity on blood platelet adhesion, a vasodilating activity, an inhibitory activity on gastric acid secretion etc. Therefore, it has been considered that PGI<sub>2</sub> is useful for the prevention and/or the treatment for thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer, hypertension etc. But its application for pharmaceuticals is limited because of its chemical instability and difficulty of separation of the actions according to purpose. Accordingly, various PGI<sub>2</sub> derivatives have been synthesized and many researches have been carried out for the maintenance and the separation of the actions. However, we have not necessarily satisfactory results yet.

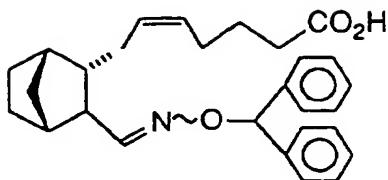
50 Recently, in order to solve two problems above described, the research for PGI<sub>2</sub> receptor agonists which have a new-typed skeleton and may be useful for the treatment of or for the prevention of the above diseases, in view of PGI<sub>2</sub> receptor level, has been carried out.

## Related Arts

55

It has been reported in the literatures, that the following compounds not having the PGI<sub>2</sub> skeleton are PGI<sub>2</sub> receptor agonists which bind to a PGI<sub>2</sub> receptor and inhibit blood platelet aggregation:

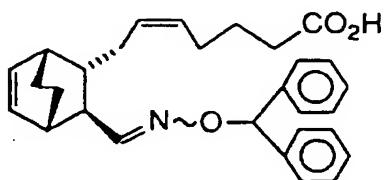
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10 (see Brit. J. Pharmacol., 76, 423(1982), *ibid*, 84, 595(1985), and the Japanese Patent Kohyo No. 55-501098),

15

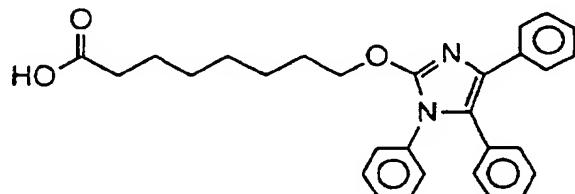
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(see Brit. J. Pharmacol., 76, 423(1982), *ibid*, 84, 595(1985), and the Japanese Patent Kohyo No. 57-501127),

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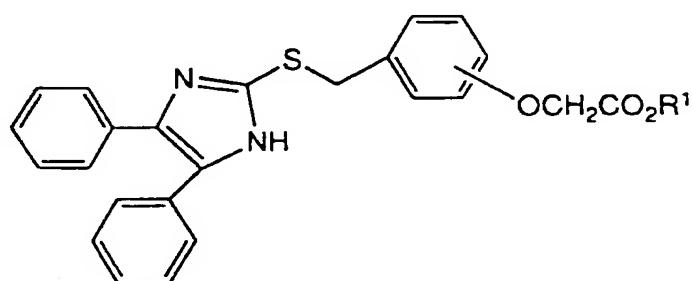


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(see Brit. J. Pharmacol., 102, 251-266(1991) and the West German Patent Publication No. 3,504,677), and

40

45



50

(see United States Patent No. 5,011,851).

#### Purpose of the Invention

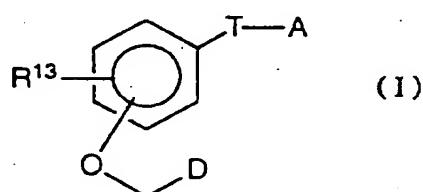
55 Energetic investigations have been carried out in order to discover new PG<sub>I2</sub> receptor agonists having a skeleton in chemical structure different from the compounds mentioned above, the present inventors have found that a kind of phenoxyacetic acid derivatives has an activity on binding to PG<sub>I2</sub> receptor and an inhibitory activity on blood platelet aggregation, and have accomplished the present invention.

The phenoxyacetic acid derivatives of the formula (I), of the present invention are quite novel, and it is not easy to predict from the above compounds already known as PG<sub>I<sub>2</sub></sub> receptor agonist, that the compounds of the present invention have an activity of PG<sub>I<sub>2</sub></sub> receptor agonist.

5 Detailed disclosure of the Invention

The present invention is related to :

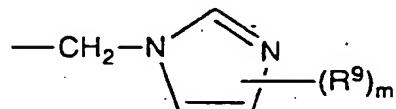
1) Phenoxyacetic acid derivatives of the formula (I):



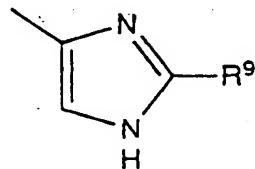
wherein

20 A is

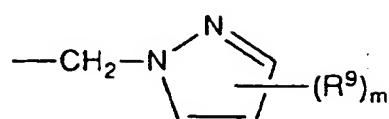
- i) -CR<sup>1</sup> = N-OR<sup>2</sup>,
- ii) -CHR<sup>1</sup>-NH-OR<sup>2</sup>,
- iii) -COE,
- iv) -SO<sub>2</sub>E,
- 25 v) -CH<sub>2</sub>-NR<sup>3</sup>-Y,
- vi) -Z-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- vii) -CH<sub>2</sub>-OR<sup>6</sup>,
- viii) -CO<sub>2</sub>R<sup>6</sup>,
- 30 ix) -CH<sub>2</sub>-O~N=CR<sup>7</sup>R<sup>8</sup>,
- x) -CH<sub>2</sub>-O-NHCHR<sup>7</sup>R<sup>8</sup>,
- xi)



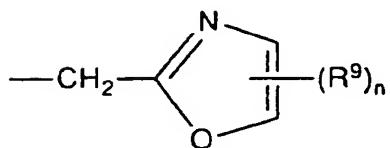
40 xii)



50 xiii)

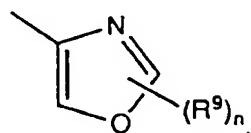


xiv)



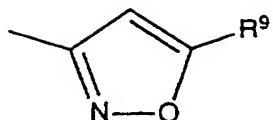
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xv)



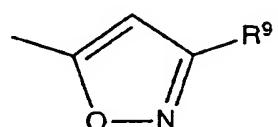
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xvi)



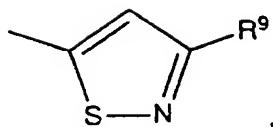
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xvii)



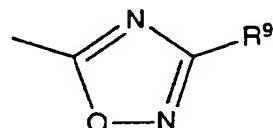
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xviii)



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xix)

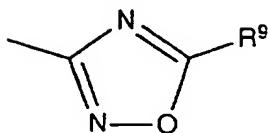


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xx)

EP 0 558 062 A2

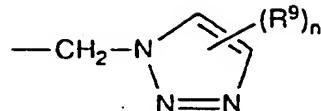
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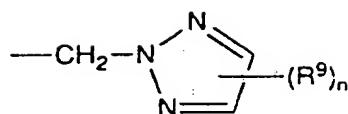
xxi)



20

25

or  
xxii)



T

is

- i) single bond,
- ii) C1-6 alkylene,
- iii) C2-6 alkenylene or
- iv) -O(CH<sub>2</sub>)<sub>s</sub>-;

D

is

- i) -CO<sub>2</sub>R<sup>10</sup> or
- ii) -CONR<sup>11</sup>R<sup>12</sup>;

30

E

is

- i) -NR<sup>4</sup>R<sup>5</sup>,
- ii) -NR<sup>3</sup>OR<sup>6</sup>,
- iii) -NR<sup>2</sup>-NR<sup>4</sup>R<sup>5</sup> or
- iv) -NR<sup>3</sup>-N=CR<sup>4</sup>R<sup>5</sup>;

35

Y

is

- i) -COR<sup>6</sup>,
- ii) -CO-L-NR<sup>4</sup>R<sup>5</sup>,
- iii) -CS-NHR<sup>4</sup> or
- iv) -SO<sub>2</sub>R<sup>6</sup>;

40

Z

is

- i) -CH=N- or
- ii) -CH<sub>2</sub>-NR<sup>3</sup>-;

L

is single bond or C1-4 alkylene;

R<sup>1</sup>

is hydrogen, C1-6 alkyl or phenyl;

50

R<sup>2</sup>

is

- i) C1-8 alkyl substituted by one or two of phenyl, 4-7 membered monocyclic hetero ring containing one nitrogen or C4-7 cycloalkyl,
- ii) C10-15 hydrocarbon condensed tricyclic ring or
- iii) C1-15 alkyl;

55

R<sup>3</sup>

is hydrogen, C1-6 alkyl or phenyl;

R<sup>4</sup> and R<sup>5</sup>

each, independently, is

- i) hydrogen,
- ii) phenyl,

EP 0 558 062 A2

iii) 4-7 membered monocyclic hetero ring containing one nitrogen or  
 iv) C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;

5 R<sup>6</sup> is  
 i) phenyl,  
 ii) 4-7 membered monocyclic hetero ring containing one nitrogen or  
 iii) C1-4 alkyl substituted by one to three of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;

10 R<sup>7</sup> is  
 i) hydrogen,  
 ii) C1-8 alkyl,  
 iii) phenyl or C4-7 cycloalkyl,  
 iv) 4-7 membered monocyclic hetero ring containing one nitrogen or  
 v) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;

15 R<sup>8</sup> is  
 i) C1-8 alkyl,  
 ii) phenyl or C4-7 cycloalkyl  
 iii) 4-7 membered monocyclic hetero ring containing one nitrogen or  
 iv) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;

20 R<sup>9</sup> is  
 i) hydrogen,  
 ii) phenyl,  
 iii) C1-4 alkyl or  
 iv) C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;

25 R<sup>10</sup> is hydrogen or C1-12 alkyl;  
 R<sup>11</sup> and R<sup>12</sup> each, independently, is hydrogen or C1-4 alkyl or  
 30 R<sup>11</sup> and R<sup>12</sup>, taken together with nitrogen bond to R<sup>11</sup> and R<sup>12</sup> is the residue of an amino acid;  
 R<sup>13</sup> is hydrogen, C1-4 alkyl, C1-4 alkoxy or nitro;

m is 1-3,

n is 1-2,

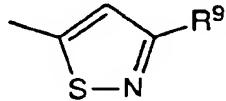
s is 2-4;

35 and the rings of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> may be also substituted by one to three of C1-C4 alkyl, C1-C4 alkoxy, halogen, nitro or trihalomethyl;

with the proviso that,

(1) when A is -SO<sub>2</sub>E wherein E is the same meaning hereinbefore defined, T is not single bond and C1 alkylene (methylene),

40 (2) when A is



wherein R<sup>9</sup> is the same meaning hereinbefore defined, T is not C2-6 alkenylene; and non-toxic salts thereof and non-toxic acid addition salts thereof.

50 2) Process for the preparation of them and

3) Pharmaceutical agent containing them as active ingredient.

Unless otherwise, specified all isomers are included in the invention. For example, alkyl, alkoxy, alkylene and alkenylene includes straight and branched ones. Double bond in alkenylene and oxime include E, Z and EZ mixture. Isomers generated by asymmetric carbon(s) e.g. branched alkyl are included in the present invention.

55 The compounds of the formula (I) of the present invention, wherein R<sup>10</sup> is hydrogen may be converted into the corresponding salts by methods known per se. Non-toxic and water-soluble salts are preferable. Suitable salts, for example, are salts of alkaline metal (potassium, sodium, etc.), salts of alkaline earth metal

(calcium, magnesium, etc.), ammonium salts, salts of pharmaceutically-acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine, etc.).

5 The compounds of the formula (I) may be converted into the corresponding acid additional salts by methods known per se. Non-toxic and water-soluble salts are preferable. Suitable acid addition salts, for example, are salts of inorganic acids, e.g., hydrochloride, hydrobromide, sulphate, phosphate, nitrate etc., or salts of organic acids, e.g., acetate, lactate, tartarate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethioate, glucuronate, gluconate etc.

10 The compounds of the formula (I), salts thereof or acid additional salts thereof may be converted into hydrate thereof by methods known per se.

15 In the formula (I), C1-4 alkylene represented by L means methylene, ethylene, trimethylene, tetramethylene and isomeric groups thereof. C1-6 alkylene represented by T means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomeric groups thereof. C2-6 alkenylene represented by T means ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomeric groups thereof having one or two double bond.

20 In the formula (I), C1-4 alkyl represented by R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> mean methyl, ethyl, propyl, butyl and isomeric groups thereof. C1-6 alkyl represented by R<sup>1</sup> and R<sup>3</sup> mean methyl, ethyl, 25 propyl, butyl, pentyl, hexyl and isomeric groups thereof. C1-8 alkyl represented by R<sup>2</sup>, R<sup>7</sup> and R<sup>8</sup> mean methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric groups thereof. C1-15 alkyl represented by R<sup>2</sup> means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl and isomeric groups thereof. C1-12 alkyl represented by R<sup>10</sup> means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and isomeric groups thereof.

25 In the formula (I), C1-4 alkoxy represented by R<sup>13</sup> means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

In the formula (I), C4-7 cycloalkyl represented by R<sup>2</sup>, R<sup>7</sup> and R<sup>8</sup> mean, for example, cyclopentyl, cyclohexyl and cycloheptyl.

30 In the formula (I), 4-7 membered monocyclic hetero ring represented by R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> mean, for example, pyrrole, pyridine, azepine ring and partially or fully saturated ring thereof (e.g., pyrrolidine, piperidine ring, etc.)

In the formula (I), C10-15 hydrocarbon condensed tricyclic ring means, for example, indacene, fluorene, anthracene, dibenzocycloheptene rings and partially or fully saturated ring thereof.

35 In the formula (I), C1-C4 alkyl as substituents of the rings in R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> mean methyl, ethyl, propyl, butyl and isomers thereof. C1-C4 alkoxy mean methoxy, ethoxy, propoxy, butoxy and isomers thereof. Halogen and halogen in trihalomethyl mean fluorine, chlorine, bromine and iodine atoms.

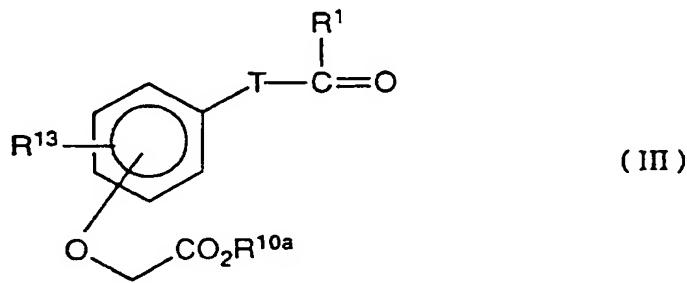
Example of representative compounds of the formula (I), of the present invention are listed as follows:

- (1) 3-[2-(2-Phenyl-2-(3-pyridyl)ethyl]oxyiminoethyl]phenoxyacetic acid,
- (2) 3-[2-(2-Cyclohexyl-2-phenylethyl]oxyiminoethyl]phenoxyacetic acid,
- 40 (3) 3-[2-(2-Fluorene-9-yl)ethyl]oxyiminoethyl]phenoxyacetic acid,
- (4) 3-[2-(2-Phenyldecyl)oxyiminoethyl]phenoxyacetic acid,
- (5) 4-(2-Benzoylaminoethyl)phenoxyacetic acid,
- (6) 4-[2-(N,N-Diphenylaminocarbonylamino)ethyl]phenoxyacetic acid,
- (7) 4-[2-(N,N-Diphenylaminomethylcarbonylamino)ethyl]phenoxyacetic acid,
- 45 (8) 4-(2-Phenylaminothiocarbonylaminoethyl)phenoxyacetic acid,
- (9) 4-(2-Phenylsulfonylaminoethyl)phenoxyacetic acid,
- (10) 4-[2-(N,N-Diphenylaminocarbonylaminoimino)ethyl]phenoxyacetic acid,
- (11) 3-[3-(2-Diphenylmethylimidazol-5-yl)propyl]phenoxyacetic acid,
- (12) 3-[3-(3,4,5-Triphenylpyrazol-1-yl)propyl]phenoxyacetic acid,
- 50 (13) 3-[3-(Oxazol-2-yl)propyl]phenoxyacetic acid,
- (14) 3-[3-(5-Ethyloxazol-4-yl)propyl]phenoxyacetic acid,
- (15) 3-[3-(5-Di(3-pyridyl)methylisoxazol-3-yl)propyl]phenoxyacetic acid,
- (16) 3-[3-(4,5-Diphenylimidazolyl)propyl]phenoxyacetic acid,
- (17) 3-[3-(5-Diphenylmethylisoxazol-3-yl)propyl]phenoxyacetamide,
- 55 (18) Amide of 3-[3-(5-Diphenylmethylisoxazol-3-yl)propyl]phenoxyacetic acid with glycine,
- (19) Octyl 3-[3-(5-diphenylmethylisoxazol-3-yl)propyl]phenoxyacetate,
- (20) 3-[3-[4-Di(3-pyridyl)methylpyrazol-1-yl]propyl]phenoxyacetic acid,
- (21) 2-Methyl-3-[3-[4-[1-phenyl-1-(3-pyridyl)methyl]pyrazol-1-yl]propyl] phenoxyacetic acid,

- (22) 3-[3-Di(3-pyridyl)methyloxyiminopropyl]phenoxyacetic acid,  
 (23) 3-[3-[Di(3-pyridyl)methylideneaminoxy]propyl]phenoxyacetic acid,  
 (24) 3-[3-[1-cyclohexyl-1-Phenylmethylideneaminooxy]propyl]phenoxyacetic acid,  
 (25) 2-Methyl-3-[3-[1-phenyl-1-(3-pyridyl)methylideneaminoxy]propyl] phenoxyacetic acid,  
 (26) 3-(3-Diphenylmethyloxyaminosulfonylpropyl)phenoxyacetic acid.  
 (27) 3-[3-[(N,N-Diphenylamino)aminosulfonyl]propyl]phenoxyacetic acid,  
 (28) 3-[3-[(1,1-Diphenylmethylideneamino)aminosulfonyl]propyl]phenoxy acetic acid,  
 (29) 4-[2-[(N,N-Diphenylaminocarbonylamino)amino]ethyl]phenoxyacetic acid,  
 (30) 3-[3-[5-[1-Phenyl-1-(3-pyridyl)methyl]isoxazol-3-yl]propyl]phenoxyacetic acid,  
 (31) 3-[4-Methyl-4-(1-phenyl-1-(3-pyridyl)methyloxyimino)butyl]phenoxyacetic acid,  
 (32) 3-[2-[4-(1-Phenyl-1-(3-pyridyl)methyl)pyrazol-1-yl]ethyl]phenoxyacetic acid,  
 (33) 3-[3-[1-Phenyl-1-(3-pyridyl)methylaminoxy]propyl]phenoxyacetic acid, non-toxic salts thereof and  
 non-toxic acid addition salts thereof and those description in examples below.

15 Process for the preparation

The compounds of the present invention of the formula (I), may be prepared  
 (i) by reacting a compound of the formula (III):

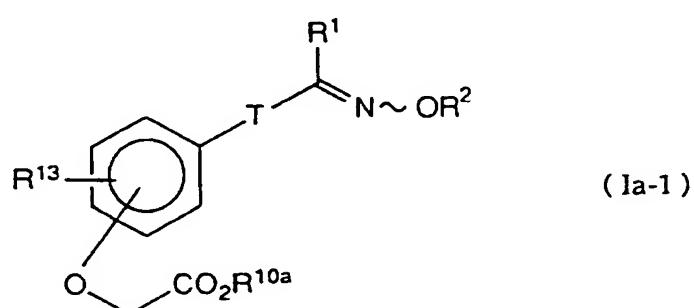


wherein R<sup>10a</sup> means methyl or ethyl and the other symbols are the same meaning as hereinbefore defined, with a compound of the formula (a):

35 R<sup>2</sup>ONH<sub>2</sub> (a)

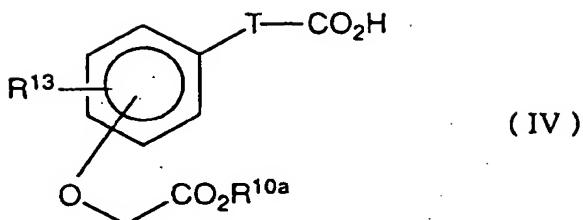
wherein R<sup>2</sup> is the same meaning as hereinbefore defined,

(ii) by subjecting a compound obtained by reaction (i) of the formula (Ia1):



wherein all the symbols are the same meaning as hereinbefore defined, to reduction,  
 (iii) by amidation of a compound of the formula (IV):

5



(IV)

10

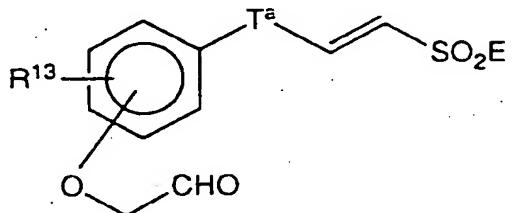
wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (b):

15

H E (b)

wherein E is the same meaning as hereinbefore defined,  
(iv) by subjecting a compound of the formula (VI):

20

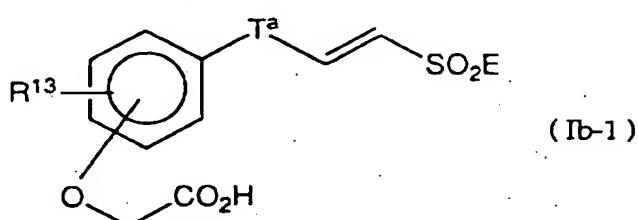


(VI)

25

wherein  $T^a$  is single bond, C1-4 alkylene, C2-4 alkenylene, or  $-\text{O}-(\text{CH}_2)_t-$ , wherein t is 0-2, and the other symbols are the same meaning as hereinbefore defined, to Jone's oxidation,  
(v) by subjecting a compound obtained by reaction (iv) of the formula (Ib-1):

35

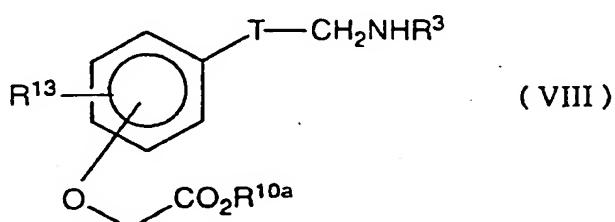


(Ib-1)

40

wherein all the symbols are the same meaning as hereinbefore defined, to hydrogenation (including a series of reactions subjecting a compound of the formula (Ib-1) to methylesterification, and to hydrogenation, followed by hydrolysis of the ester bond, for the convenience of purification),  
(vi) by amidation or thioamidation of a compound of the formula (VIII):

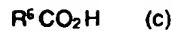
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(VIII)

55

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (c):



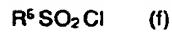
5 wherein  $R^6$  is the same meaning as hereinbefore defined, or with a compound of the formula (d):



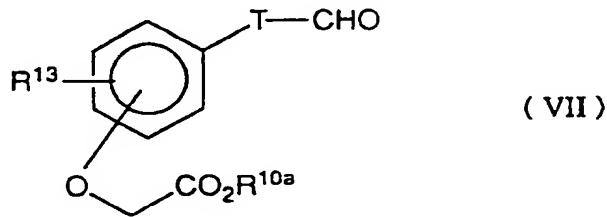
10 wherein all the symbols are the same meaning as herein before defined, or with a compound of the formula (e):



15 wherein  $R^4$  is the same meaning as hereinbefore defined, or with a compound of the formula (f):



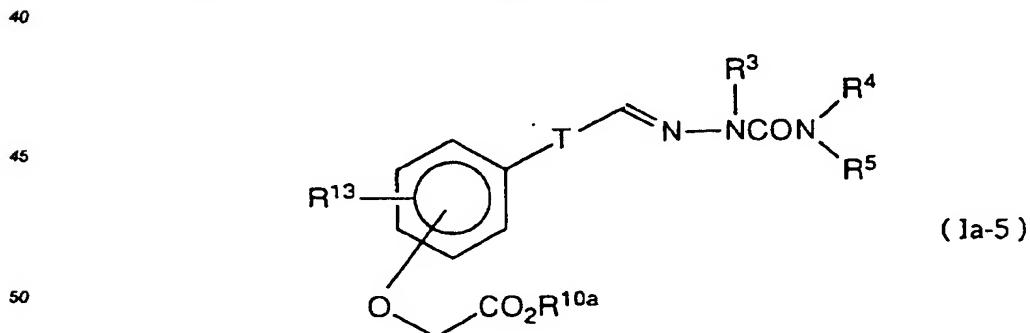
20 wherein  $R^6$  is the same meaning as hereinbefore defined,  
(vii) by reacting a compound of the formula (VII):



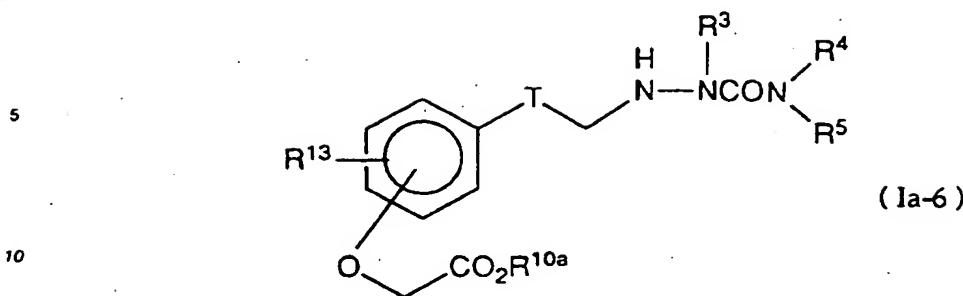
wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (g):



wherein all the symbols are the same meaning as hereinbefore defined,  
(viii) by subjecting a compound obtained by reaction (vii) of the formula (Ia-5):



55 wherein all the symbols are the same meaning as hereinbefore defined, to reduction,  
(ix) by reacting of the compound obtained by reaction (viii) of the formula (Ia-6):

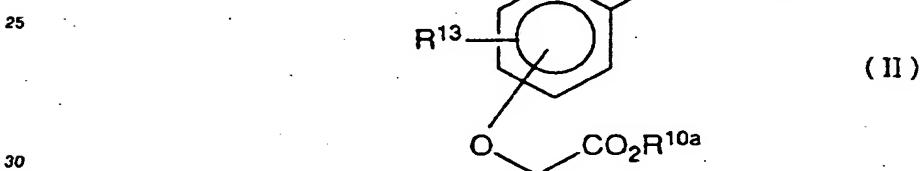


15 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (h):

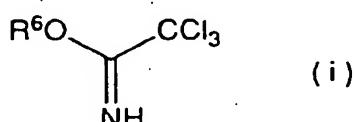
R<sup>3a</sup>I (h)

wherein R<sup>3a</sup> is C1-6 alkyl or phenyl,

20 (x) by reacting of the compound of the formula (II):



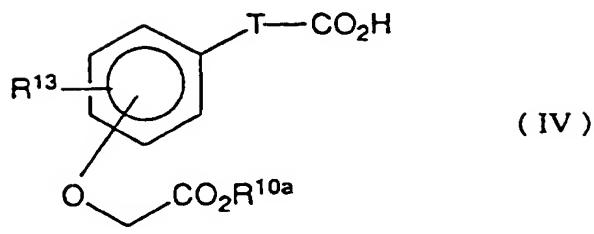
35 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (i):



45 wherein R<sup>6</sup> is the same meaning as hereinbefore defined, or with a compound of the formula (s):

R<sup>6</sup>X (s)

50 wherein X is halogen and R<sup>6</sup> is the same meaning as hereinbefore defined.  
(xi) by esterification of a compound of the formula (IV):

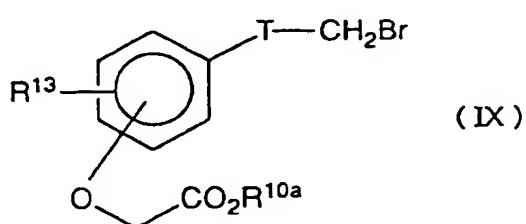


wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (j):

15 R<sup>6</sup>OH (j)

wherein R<sup>6</sup> is the same meaning as hereinbefore defined,  
(xii) by reacting of a compound of the formula (IX):

20



30

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (k):

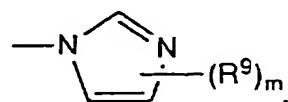
35 G H (k)

wherein

G is

i)

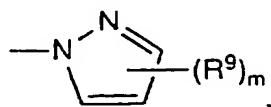
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ii)

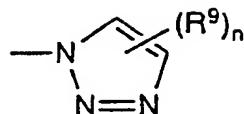
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iii)

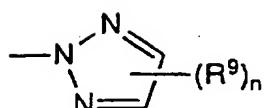
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or  
iv)

10

15



wherein all the symbols are the same meaning as hereinbefore defined, or with a compound of the formula (q):

20



wherein all the symbols are the same meaning as hereinbefore defined, or with a compound of the formula (r):

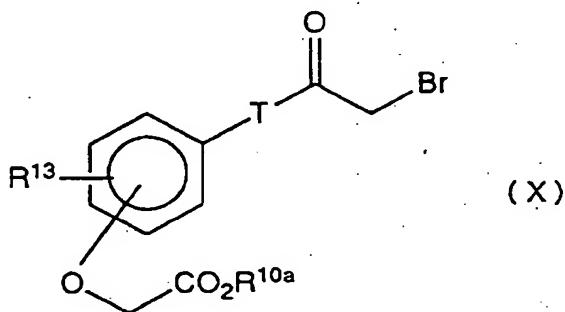
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wherein all the symbols are the same meaning as hereinbefore defined,  
(xiii) by reacting of a compound of the formula (x):

30

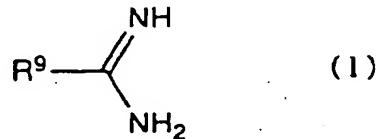
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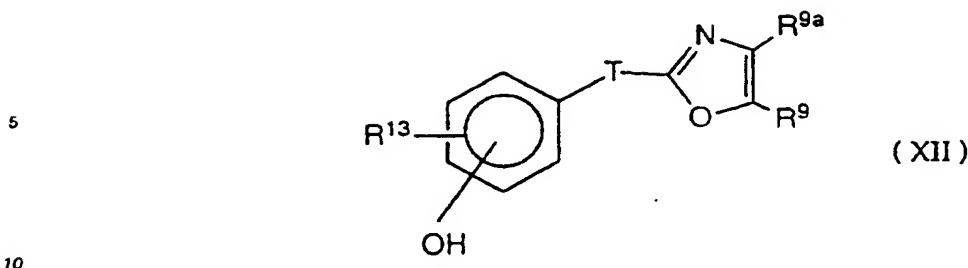
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wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (I):

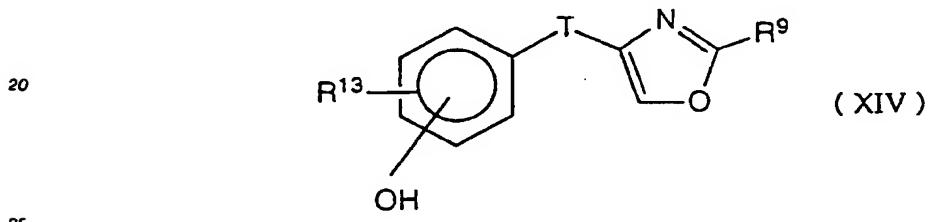
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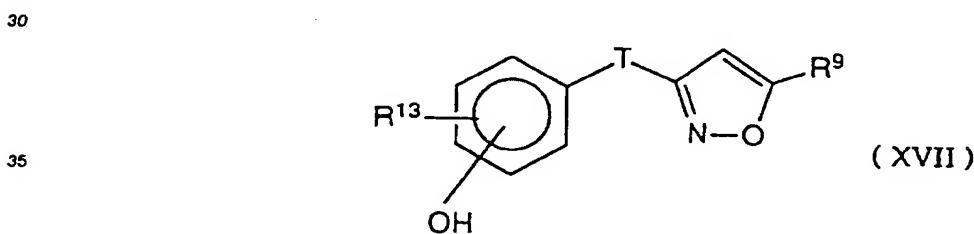
wherein  $\text{R}^9$  is the same meaning as hereinbefore defined,  
(xiv) by reacting of a compound of the formula (XII):



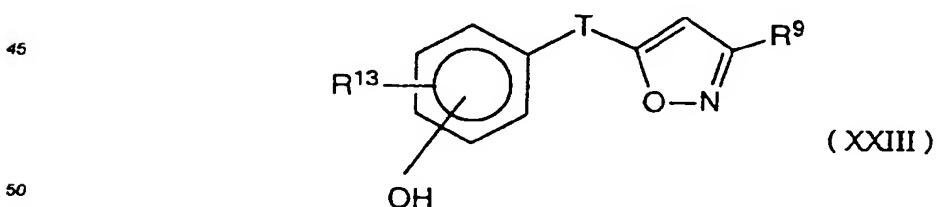
wherein R<sup>9a</sup> is phenyl, C1-4 alkyl or C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen and the other symbols are the same meaning as hereinbefore defined, or  
15 a compound of the formula (XIV):



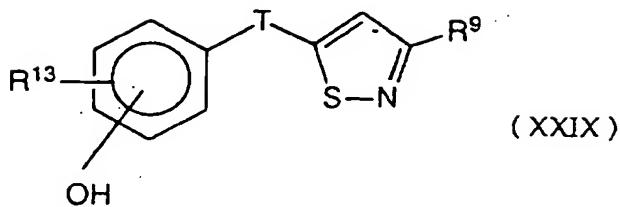
wherein all the symbols are the same meaning as hereinbefore defined, or a compound of the formula (XVII):



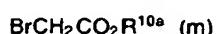
40 wherein all the symbols are the same meaning as hereinbefore defined, or a compound of the formula (XXIII):



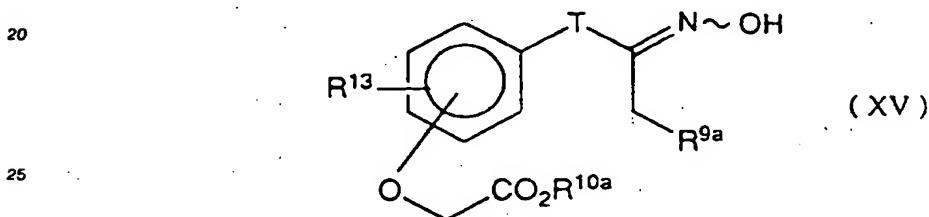
wherein all the symbols are the same meaning as hereinbefore defined, or a compound of the formula (XXIX):



10 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula  
(m):



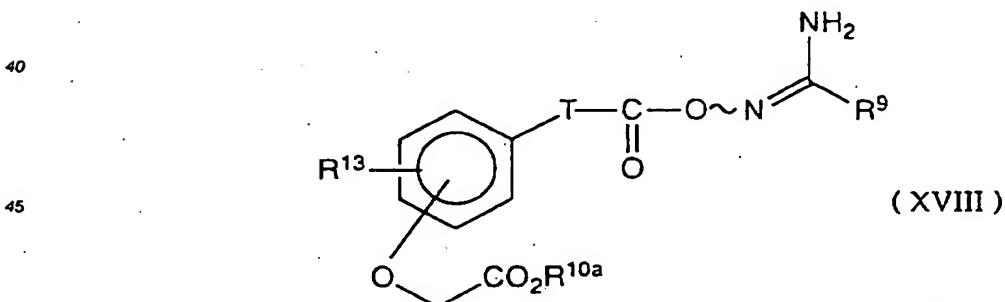
15 wherein R<sup>10a</sup> is the same meaning as hereinbefore defined,  
(xv) by reacting of a compound of the formula (XV):



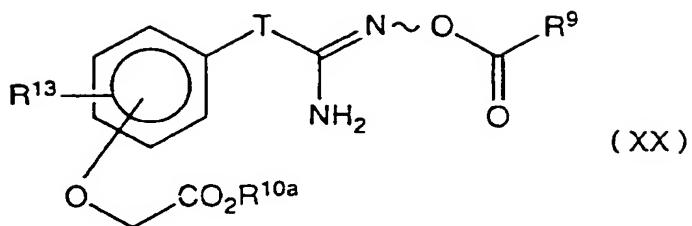
25 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula  
(n):



30 wherein R<sup>9</sup> is the same meaning as hereinbefore defined,  
35 (xvi) by cyclization of a compound of the formula (XVIII):



50 wherein all the symbols are the same meaning as hereinbefore defined,  
(xvii) by cyclization of a compound of the formula (XX):



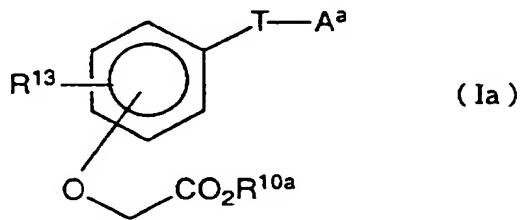
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wherein all the symbols are the same meaning as hereinbefore defined.

(xvii) by hydrolysis of the compound obtained by hereinbefore reaction (i), (ii), (iii), (vi), (vii), (viii), (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xvi) or (xvii) of the formula (Ia):

15

20



25

wherein

Aa is

- i) ;CR<sup>1</sup> = N-OR<sup>2</sup>,
- ii) -CHR<sup>1</sup>-NH-OR<sup>2</sup>,
- iii) -COE,
- iv) -CH<sub>2</sub>NR<sup>3</sup>-Y,
- v) -CH=N-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- vi) -CH<sub>2</sub>-NH-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- vii) -CH<sub>2</sub>-NR<sup>3a</sup>-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- viii) -CH<sub>2</sub>OR<sup>6</sup>,
- ix) -CO<sub>2</sub>R<sup>6</sup>,
- x) -CH<sub>2</sub>G,
- xi) -CH<sub>2</sub>-O-N = CR<sup>7</sup>R<sup>8</sup>,
- xii) -CH<sub>2</sub>-O-NHCHR<sup>7</sup>R<sup>8</sup>,
- xiii)

30

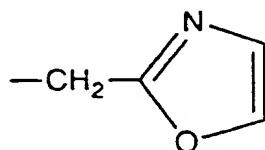
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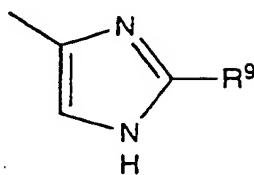
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xiv)

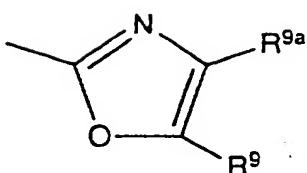
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xv)

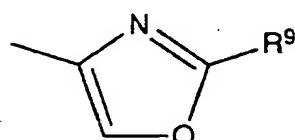
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xvi)

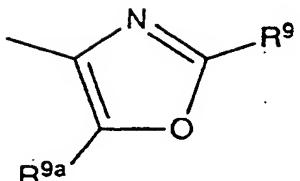
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xvii)

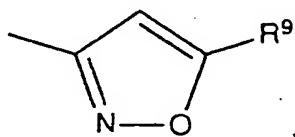
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xviii)

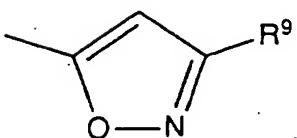
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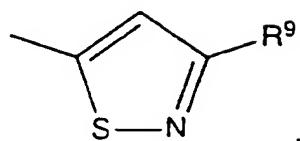
xix)

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xx)

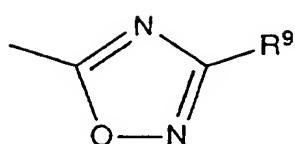
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xxi)

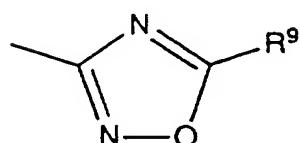
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or  
xxii)

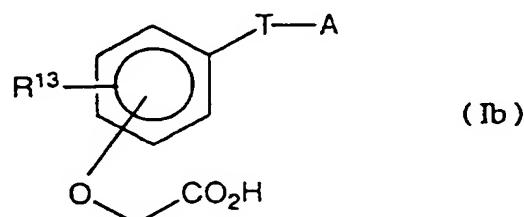
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and the other symbols are the same meaning as hereinbefore defined,  
(xix) by esterification of the compound obtained by hereinbefore reaction (iv), (v) or (xviii) of the formula  
(Ib):

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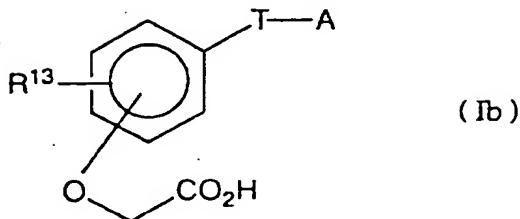
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wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (o):

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$R^{10b}OH$  (o)  
wherein  $R^{10b}$  is C1-12 alkyl, or  
(xx) by amidation of the compound obtained hereinbefore reaction (iv), (v), or xviii) of the formula (Ib):

55



wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (p):

$R^{11}R^{12}NH$  (p)

15

wherein all the symbols are the same meaning as hereinbefore defined.

The reaction (i) is known, for example, it may be carried out in an inert organic solvent (tetrahydrofuran (THF), methanol, ethanol, dimethoxyethane, dioxane or two or more of the mixture, etc.) at 0-70 °C.

20 The reaction (ii) and (viii) are known, for example, they may be carried out in a water miscible organic solvent (THF, dioxane, methanol, ethanol, dimethoxyethane or two or more of the mixture, etc.), in the presence of an acid (hydrochloric acid, acetic acid, trifluoroacetic acid, etc.), using a reducing agent (sodium cyanoborohydride, etc.) at 0-70 °C.

25 The reaction (iii) and (vi) are known, for example, they may be carried out in an inert organic solvent (methylene chloride, etc.), in the presence of an appropriate condensing agent (2-chloro-N-methylpyridinium iodide, etc.) and a proper base (triethylamine, N,N-dimethylaminopyridine or two or more of the mixture, etc.) at 0-40 °C.

The reaction (iv) is known, for example, it may be carried out in acetone using a Jone's agent at -10-40 °C.

30 The reaction (v) is known, for example, it may be carried out in an inert organic solvent (THF, diethylether, dioxane, ethyl acetate, methanol, ethanol, methylene chloride, etc.) using a catalyst (palladium on carbon, palladium, hydroxy palladium, palladium acetic acid, palladium black, platinum black, etc.) at normal or elevated pressure of hydrogen gas, at 0-80 °C.

35 The reaction may be carried out, for the convenience of purification, the compound of the formula (Ib-1) reacted to methylestification, and to hydrogenation, following hydrolysis of ester bond. The methylestification is known, for example, it may be carried out in an inert organic solvent (diethylether, ethyl acetate, etc.) using diazomethane at 0-10 °C. And the hydrolysis of ester bond may be carried out by the same procedure as hereafter defined for the reaction (xviii).

40 The reaction (vii) is known, for example, it may be carried out in an inert organic solvent (methanol, ethanol, etc.) under an atmosphere of inert gas at 0-40 °C.

45 The reaction (ix) is known, for example, it may be carried out in an inert organic solvent (N,N-dimethylformamide (DMF), etc.), in the presence or absence of an appropriate base (sodium hydride, etc.).

The reaction (x) is known, for example, it may be carried out in an inert organic solvent (chloroform, cyclohexane or two or more of the mixture, etc.), in the presence of the Lewis acid (trifluoroborane etherate, etc.), or in an inert organic solvent (DMF, etc.), in the presence of an amine (N,N-dimethylaminopyridine, triethylamine, pyridine, etc.) at 0 °C - a reflux temperature.

50 The reaction (xi) is known, for example, it may be carried out in an inert organic solvent (methylene chloride, etc.), in the presence of an appropriate condensing agent (2-chloro-N-methylpyridinium iodide, etc.) and a proper base (triethylamine, N,N-dimethylaminopyridine or two or more of the mixture etc.) at 0-40 °C.

The reaction (xii) is known, for example, it may be carried out in inert organic solvent (DMF, THF, etc.), in Present of an appropriate base (sodium hydride, potassium t-butoxide, n- butyllithium, etc.).

The reaction (xiii) is known, for example, it may be carried out in an inert organic solvent (chloroform, etc.) at 0 °C - a reflux temperature.

The reaction (xiv) is known, for example, it may be carried out in an inert organic solvent (DMF, acetone, etc.), in the presence of an appropriate base (potassium carbonate, etc.) at 0-50 °C.

55 The reaction (xv) is known, it may be carried out at 80-135 °C without an organic solvent.

The reaction (xvi) and (xvii) are known, for example, they may be carried out in an inert organic solvent (trueno, etc.) at 0 °C - a reflux temperature.

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The reaction (xviii) is known, for example, it may be carried out in an inert organic solvent (methanol, ethanol, dioxane, THF, dimethoxyethane or two or more of the mixture, etc.) using an aqueous solution of an alkaline (potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, etc.) at 0- 50 °C

5 The reaction (xix) and (xx) are known, for example, they may be carried out by reacting a compound of the formula (I6) in an inert organic solvent (methylene chloride, etc.) with an acyl halide such as oxalyl chloride, thionyl chloride, and then by reacting a compound thus obtained with an alcohol of the formula (o) or an amine of the formula (p), respectively, in an inert organic solvent (methylene chloride, etc.), in the presence of an appropriate base (triethylamine, etc.) at 0-40 °C.

10 Compounds of the formula (III), (VI), (VIII), (IX), (X), (XII), (XIV), (XV), (XVII), (XVIII) and (XX) may be prepared by using a series of reactions depicted in the following scheme.

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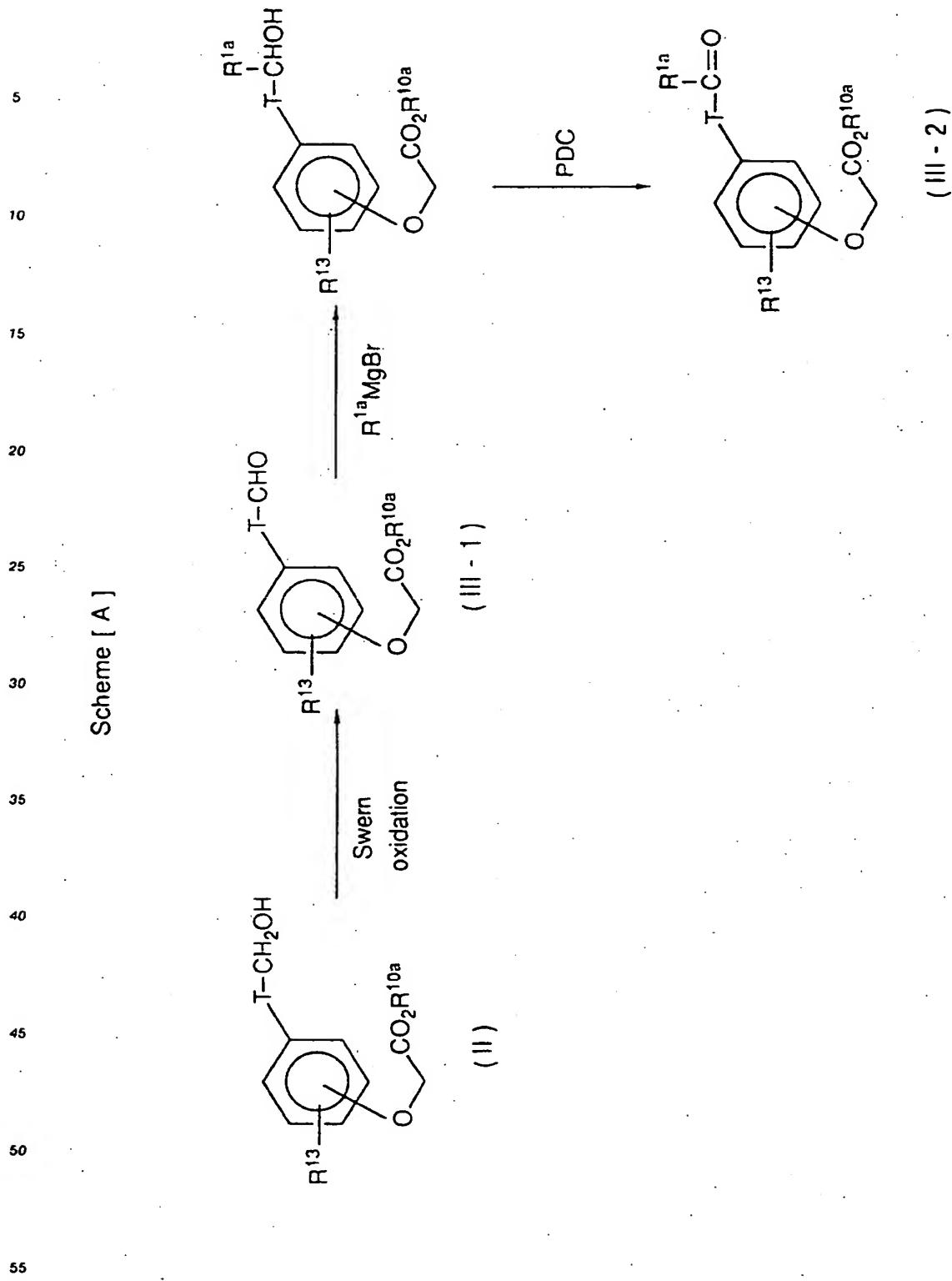
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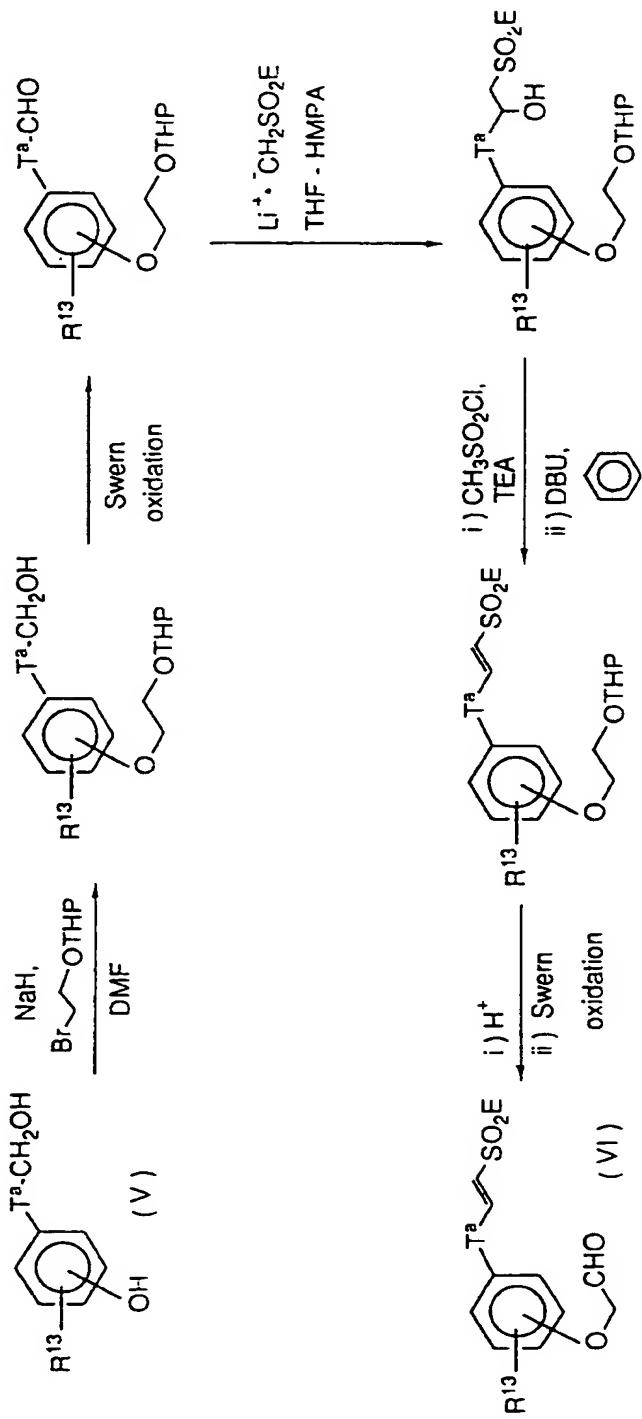
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Scheme [ A ]

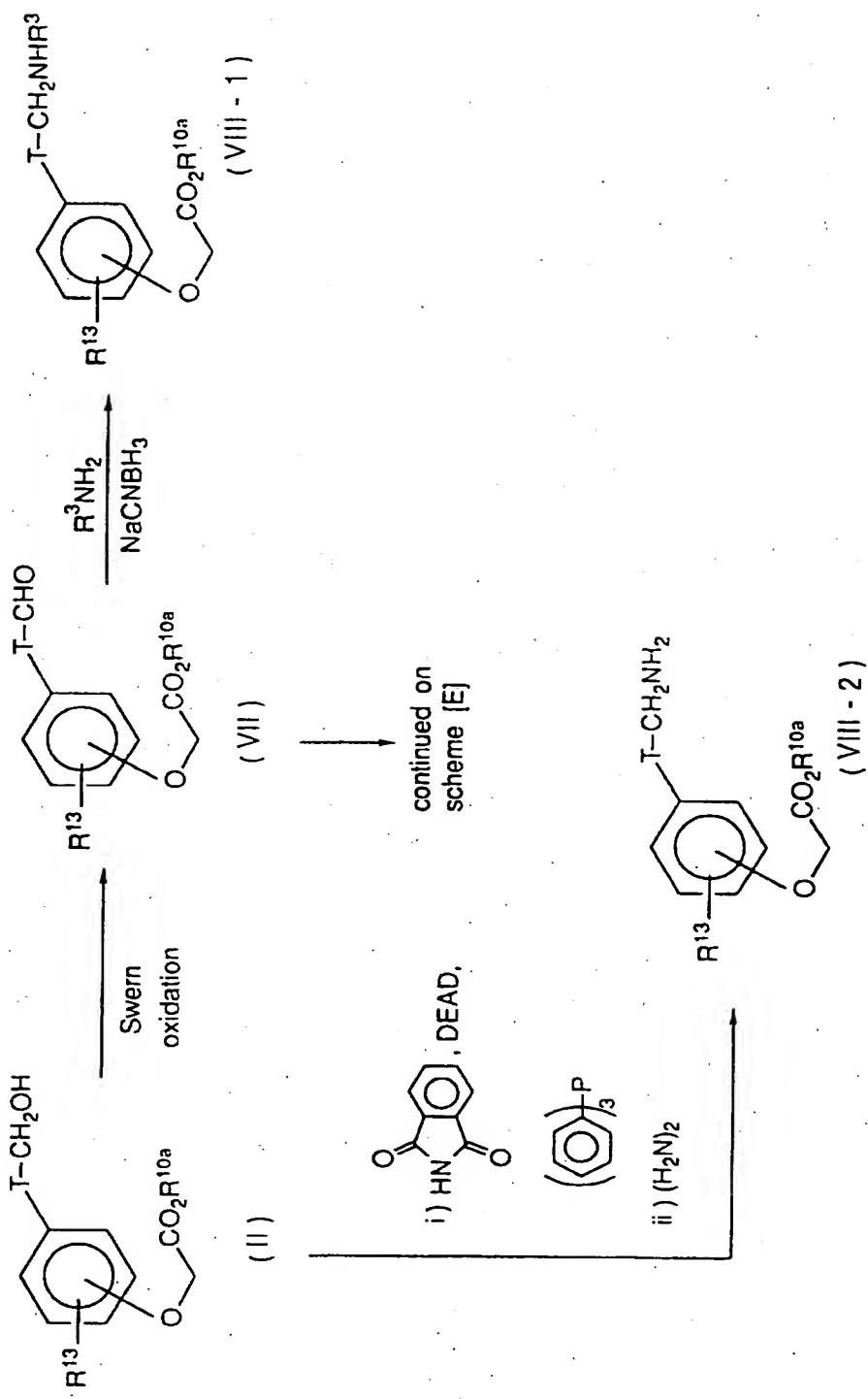


Scheme [ B ]



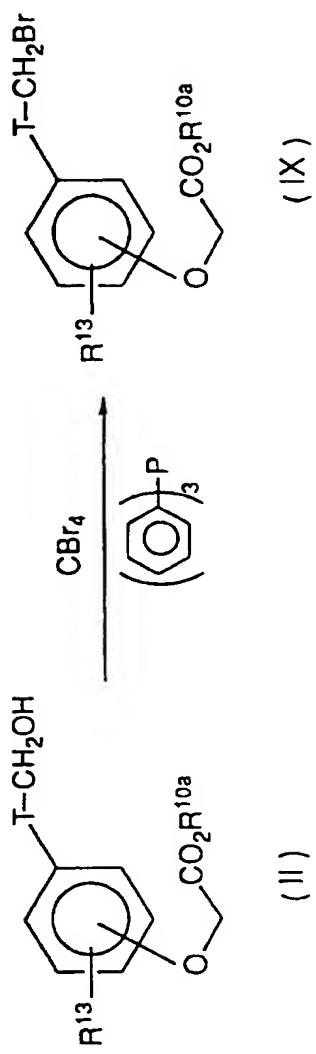
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Scheme [ C ]



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Scheme [ D ]



Scheme [ E ]

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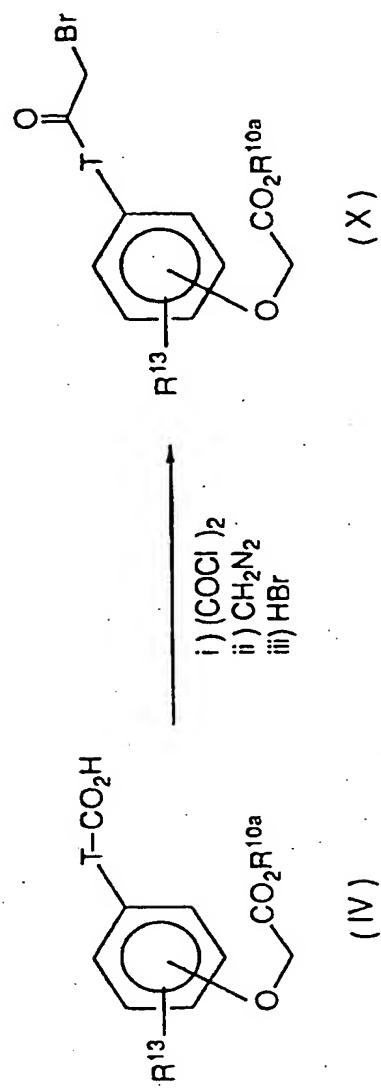
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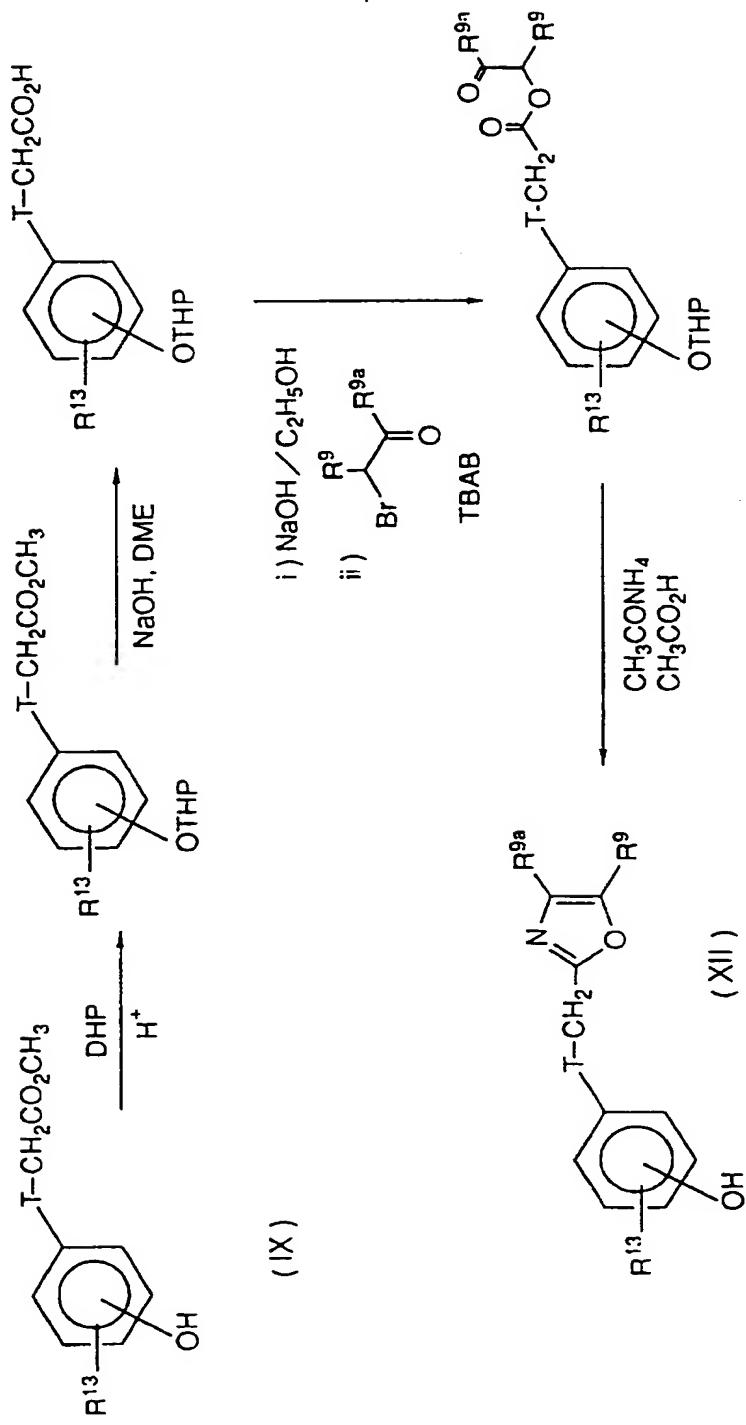
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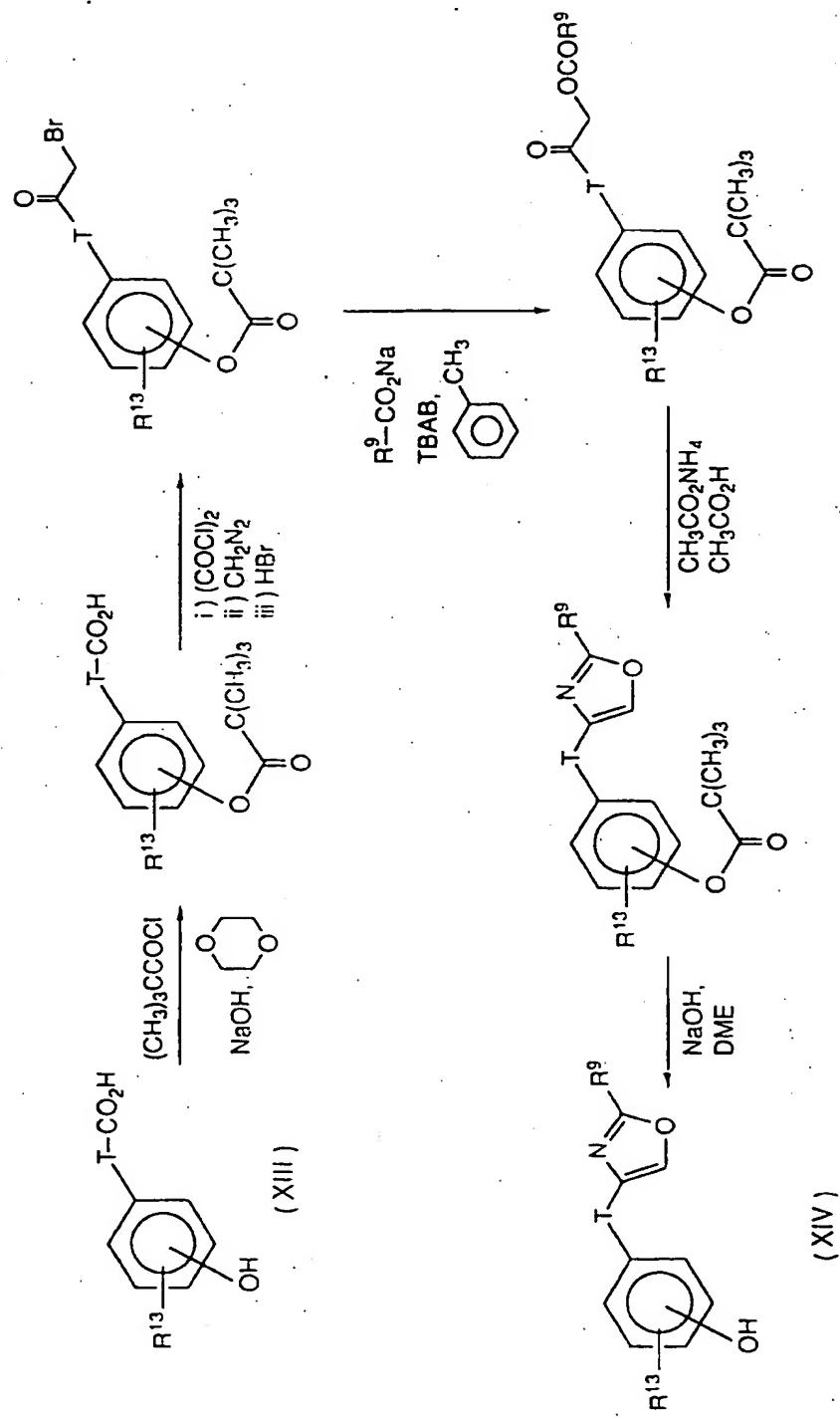


Scheme [ F ]

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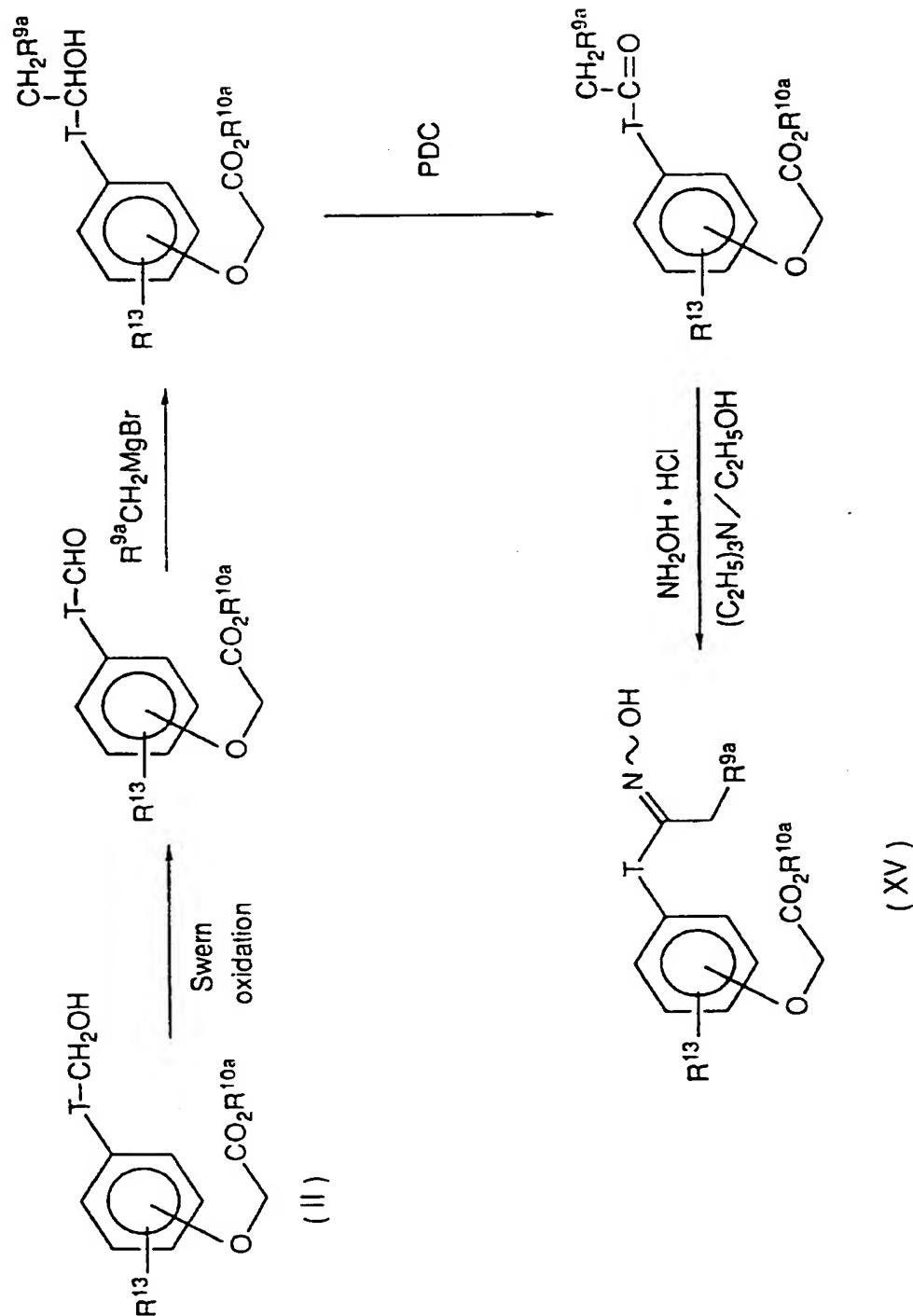


Scheme [G . 1]



Scheme [ G - 2 ]

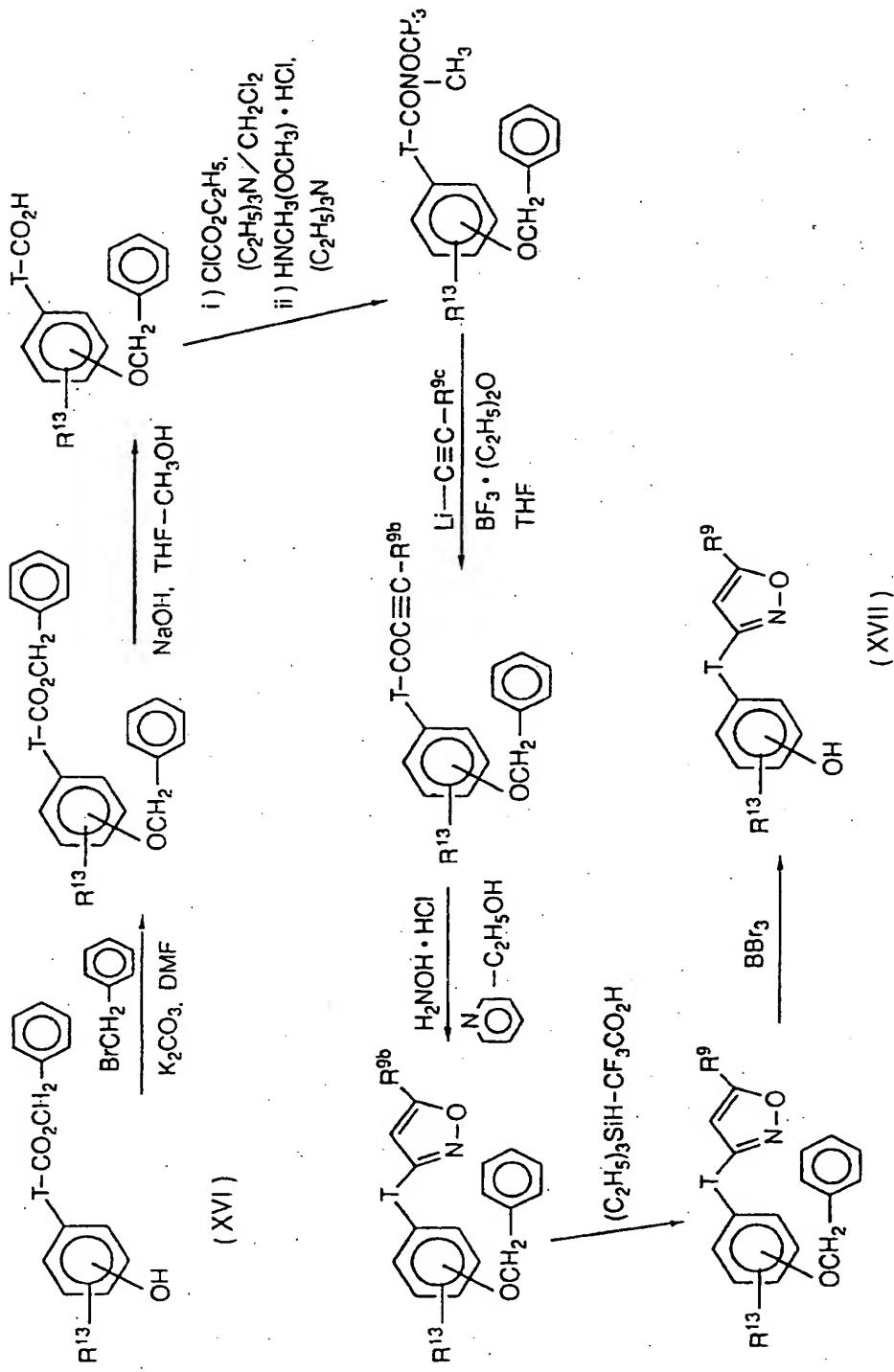
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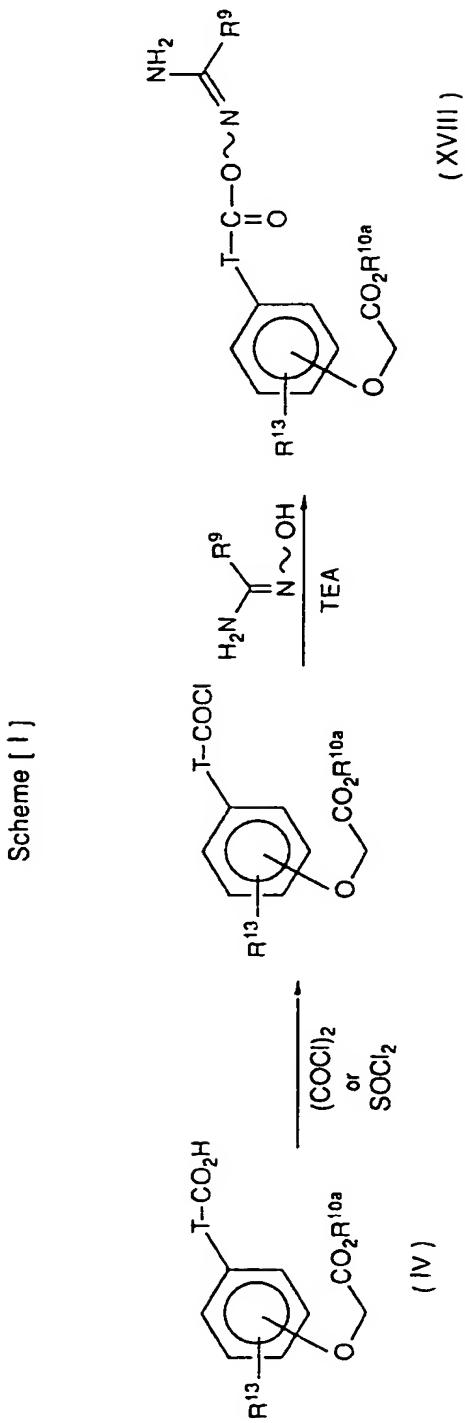
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Scheme [H]



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Scheme [ I ]



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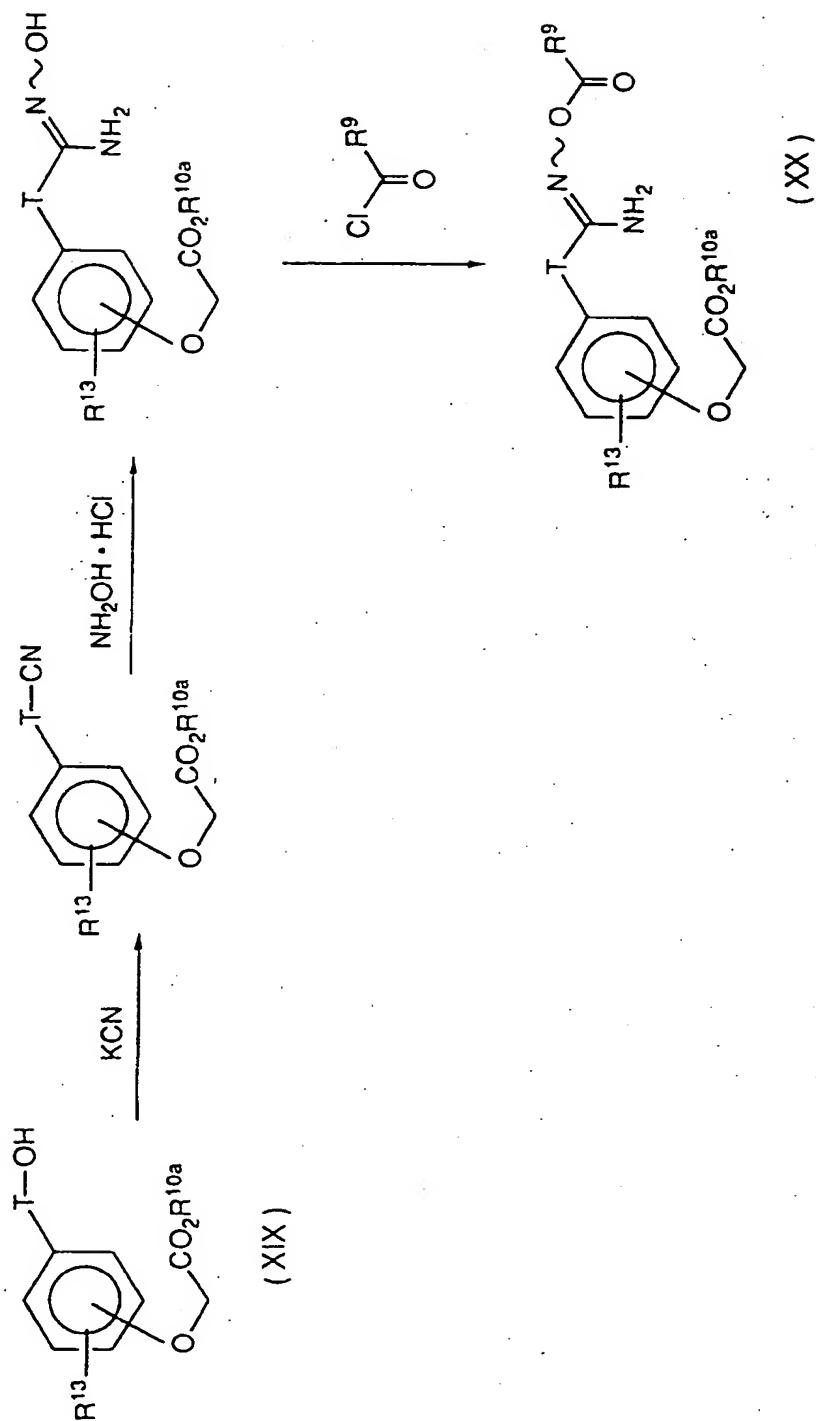
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Scheme [ J ]

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In the scheme,

55 R<sup>8b</sup>

IS

- (i) hydrogen,
- (ii) phenyl,
- (iii) C1-4 alkyl or

(iv) C1-4 alkyl substituted by one or two rings optionally selected from phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen and/or one hydroxy;

$R^{9c}$  is same meaning as  $R^{9b}$  provided that the hydroxy in  $R^{9b}$  should be replaced by -OLi; and the other symbols are the same meaning as hereinbefore defined;

5 PDC is pyridinium dichromate,

THP is tetrahydropyran-2-yl;

DMF is N,N-dimethylformamide;

THF is tetrahydrofuran;

HMPA is hexamethylphosphoramide,

10 TEA is triethylamine;

DBU is 1,8-diazabicyclo [5.4.0]-7-undecene;

DEAD is diethylazocarboxylate,

DHP is dihydropyran;

DME is dimethoxyethane; and

15 TBAB is n-tetrabutylammonium bromide.

In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of 20 reactions.

The starting materials and each reagents in process for the preparation of the present invention are known per se, or may be prepared by methods known per se.

#### Pharmacological Activities

25 It has been confirmed that the compounds of the present invention of the formula (I) possess an agonistic activity on PG<sub>I2</sub> receptor by the following experimental results.

i) Inhibitory activity on binding of [<sup>3</sup>H]-iloprost to PG<sub>I2</sub> receptor on human blood platelet membrane fraction -

#### 30 Method

50 mM Tris-HCl buffer (pH 7.4) containing 15 mM MgCl<sub>2</sub>, 5 mM EDTA and 10 nM [<sup>3</sup>H]-iloprost were used as reaction medium. To 0.2 ml of the reaction medium, human blood platelet membrane fraction (0.3 mg protein) was added with or without a test compound. The mixture was incubated at 24 °C for 30 min. After incubation, 4ml of ice-cold 10 mM Tris-HCl buffer (pH 7.4) was added to the reaction mixture, and filtered through Whatman GF/B glass fiber filter, and washed 4 times with 4 ml of ice-cold 10 mM Tris-HCl buffer (pH 7.4) to separate bound and free [<sup>3</sup>H]-iloprost. After washing, the filter was dried and radioactivity was counted. Non-specific binding was obtained by performing parallel binding experiments in the presence 40 of 10 μM non-labelled iloprost. Specific binding was calculated by subtracting the non-specific binding from the total binding.

The inhibitory effect of test compound was calculated from the following equation.

$$\text{The percentage of inhibition (\%)} = 100 - (B_1/B_0 \times 100)$$

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$B_1$  : specific [<sup>3</sup>H]-iloprost binding in presence of test compound

$B_0$  : specific [<sup>3</sup>H]-iloprost binding in absence of test compound

The results are shown in the following Table 1.

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Table 1

	Example No.	IC <sub>50</sub> ( $\mu$ M)
5	2	4.8
	4	1.6
	6	3.0
	8(l)	1.5
	8(n)	2.0
10	8(o)	0.46
	12	1.3
	15	4.0
	17	0.15
	17(b)	0.36
15	17(c)	0.27
	17(i)	0.22
	17(n)	2.0
	17(s)	0.78
	17(x)	5.0
20	17(cc)	0.26
	19	0.12
	21	4.4
	23	1.5

25

## ii) Inhibitory effect on human blood platelet aggregation

## Method

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Platelet-rich plasma (PRP) was prepared from human blood ( $5 \times 10^5$  platelets / mm<sup>3</sup>), and a test compound was added to PRP 1 min prior to the addition of ADP (4  $\mu$ M). The aggregation was monitored using a platelet aggregometer (NBS HEMA TRACER 601, Niko Bioscience, Japan).

The results are shown in the following Table 2.

35

Table 2

	Example No.	IC <sub>50</sub> ( $\mu$ M)
40	4	3.7
	8(n)	3.1
	8(o)	0.97
	12	5.0
	17	0.42
45	17(b)	0.24
	17(c)	0.47
	17(s)	3.2
	17(cc)	0.41
50	19	0.16
	23	0.37

## Toxicity

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The toxicity of the compounds of the present invention, of the formula (I) is very low and therefore, it may be confirmed that the compounds of the present invention are fully safe for pharmaceutical use.

Application for Pharmaceuticals

The compounds of the present invention, of the formula (I) possess an agonistic activity on PGI<sub>2</sub> receptor, and therefore are useful for the prevention and/or the treatment of thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer and hypertension, etc.

For the purpose above described, the compounds of the formula (I), of the present invention, non-toxic salts thereof, acid additional salts thereof and hydrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 100 µg and 100 mg, by parenteral administration up to several times per day, or continuous administration between 1 and 24 hrs. per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

When administration of the compounds of the present invention, it is used as solid compositions, liquid compositions or other compositions for oral administration, as liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc.). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate, etc.), stabilizing agents (such as lactose, etc.), and assisting agents for dissolving such as glutamic acid, etc.).

The tablets or pills may, if desired, be coated with a film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate, etc.), or be coated with more than two films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs. In such compositions, one or more of the active compound(s) is or are contained in inert diluent(s) commonly used in the art (Purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents, etc.), sweetening agents, flavouring agents, perfuming agents, and preserving agents.

Other compositions for oral administration included spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfate etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid, etc.). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entireties by reference) may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one or more of active compounds(s) is or are admixed with at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSORBATE80 (registered trade mark), etc.).

Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose, etc.), assisting agents such as assisting agents for dissolving (glutamic acid, asparaginic acid, etc.).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, and which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before used.

Other compositions for parenteral administration include liquids for external use, and endermic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by per se known methods.

## Reference examples and Examples

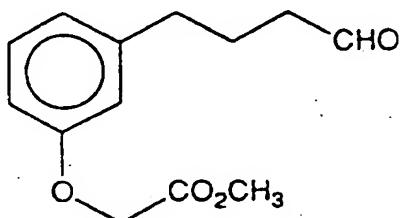
The following reference examples and examples illustrate the present invention, but not limit the present invention

- 5      The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations.  
 Unless otherwise specified, "IR" were measured by the liquid film method, and "NMR" were measured in a solution of  $\text{CDCl}_3$ .

## 10     Reference example 1

Methyl 3-(3-formylpropyl)phenoxyacetate

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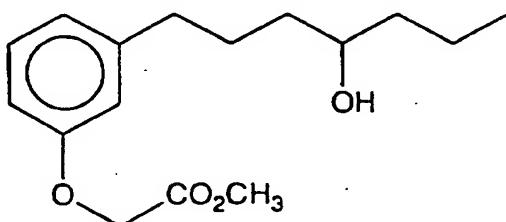
To a solution of oxalyl chloride (1.26 ml) in methylene chloride (30 ml) at -70 °C, a solution of dimethylsulfoxide (2.11 ml) in methylene chloride (3.0 ml) was added dropwise. To the obtained solution, a solution of methyl 3-(4-hydroxybutyl) phenoxyacetate (1.94 g) in methylene chloride (8.0 ml) was added dropwise. Triethylamine (6.9 ml) was added dropwise thereto while the reaction temperature was maintained at -70 °C. The reaction mixture was warmed slowly to -40 °C over a 30 min period and then quenched by addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was extracted with ether. The extract was washed with a saturated aqueous solution of ammonium chloride and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5 : 2) to give the title compound (1.41 g) having the following physical data.

TLC: Rf 0.26 (n-hexane : ethyl acetate = 2 : 1);  
 NMR: δ 9.74 (1H, s), 7.35-7.07(1H, m), 6.92-6.60 (3H, m), 4.62 (2H, s), 3.79 (3H, s), 2.63 (2H, t, J=7Hz), 2.47 (2H, t, J=8Hz), 2.10-1.92 (2H, m).

## 40     Reference example 2

Methyl 3-(4-hydroxyheptyl)phenoxyacetate

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55     To a solution of the compound prepared in reference example 1 (1.26 g) in diethyl ether (10 ml), n-propylmagnesium bromide (3.0 ml of 2M in diethyl ether) was added dropwise at -70 °C. The reaction mixture was stirred for 2h with warming still -30 °C. After quenched by addition of a saturated aqueous solution of ammonium chloride, the mixture was extracted with ether. The extract was washed with a

EP 0 558 062 A2

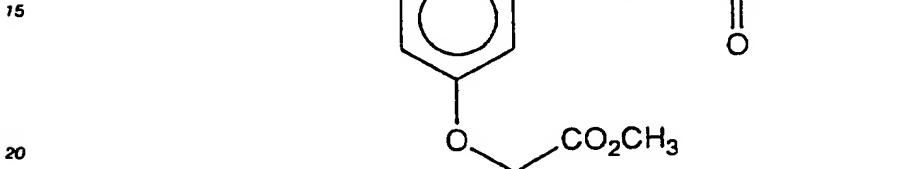
saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) to give the title compound (820 mg) having the following physical data.

TLC: Rf 0.23 (n-hexane : ethyl acetate = 2 : 1);

- 5 NMR:  $\delta$  7.36-7.08 (1H, m), 6.95-6.60 (3H, m), 4.64 (2H, s), 3.82 (3H, s), 3.80-3.50 (1H, m), 2.80-2.36 (3H, m), 2.20-1.25 (8H, m), 1.10-0.80 (3H, m).

Reference example 3

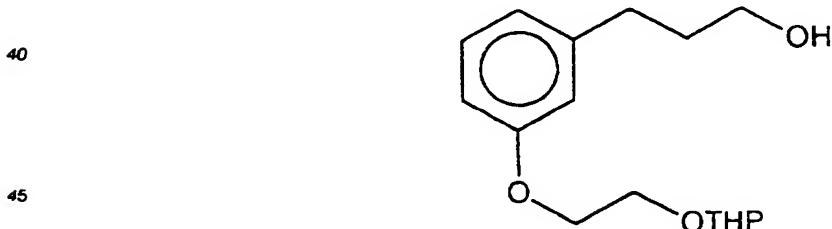
- 10 Methyl 3-(4-oxoheptyl)phenoxyacetate



- Pyridium dichromate (2.53 g) was added to a solution of the compound prepared in reference example  
25 2 (750 mg) in dimethylformamide (10 ml) at room temperature. The mixture was stirred overnight. Celite (registered trade mark) and florisil (registered trade mark) were added to the mixture. The mixture was diluted with a mixture of n-hexane-ethyl acetate (3:1)(20 ml). The mixture was filtered through florisil, the filtrate was evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5  
1) to give the title compound (350 mg) having the following physical data.  
30 TLC: Rf 0.30 (n-hexane : ethyl acetate = 3 : 1);  
NMR:  $\delta$  7.36-7.08 (1H, m), 6.90-6.60 (3H, m), 4.62 (2H, s), 3.81 (3H, s), 2.72-2.25 (6H, m), 2.10-1.38 (4H, m),  
0.90 (3H, t, J = 8Hz).

Reference example 4

- 35 3-[3-{2-(tetrahydropyran-2-yl)oxyethoxy]phenyl]propanol

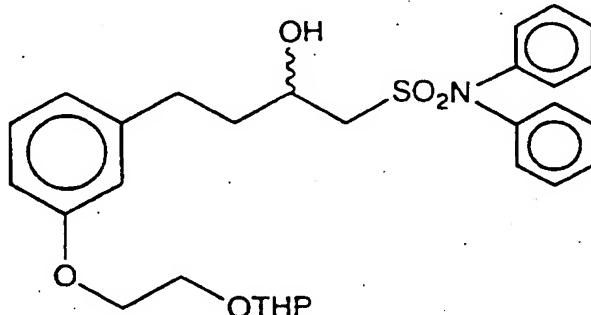


- 50 To a suspension of sodium hydride (1.84 g, 60% dispersion) in dimethylformamide (50 ml) was added dropwise a solution of 3-(3-hydroxypropyl)phenol (7.0 g) in dimethylformamide (20 ml) at 0 °C. The mixture was stirred for 1 h at room temperature. To the reaction mixture, was added 1-bromo-2-(tetrahydropyran-2-yl)ethane (5.46 g) at 0 °C. The mixture was stirred for 1 h at room temperature. After quenched by addition of water and the mixture was extracted with ether. The extract was washed with 2N aqueous solution of  
55 sodium hydroxide, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2 → 2 : 1) to give the title compound (3.36 g) having the following physical data.

TLC: R<sub>f</sub> 0.17 (ethyl acetate : n-hexane = 1 : 2);IR(cm<sup>-1</sup>): ν 3369, 2930, 1584, 1488, 1451, 1384, 1353, 1260, 1202, 1125, 1034, 992, 874, 814, 777, 695

## Reference example 5

1-[2-(Tetrahydropyran-2-yl)oxyethoxy]-3-(3-hydroxy-4-diphenylamino sulfonylbutyl)benzene



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To a solution of N,N-diphenylsulfonamide (0.99 g) in a mixture of tetrahydrofuran-hexamethylphosphoramide (20:3) (23 ml) was added dropwise n-butyllithium (3.75 ml of 1.6 M in n-hexane) at -78 °C.

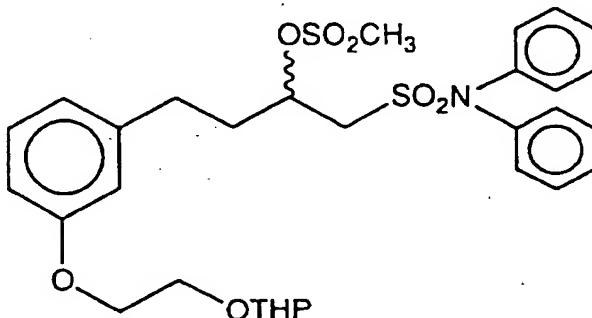
The mixture was stirred for 30 min at -78 °C. To the mixture obtained was added a solution of a compound (which was prepared by the same procedure as reference example 1, using the compound prepared in reference example 4) (1.11 g) in tetrahydrofuran (10 ml). The reaction mixture was stirred for 1 h at -78 °C. After quenched by addition of water and the mixture was extracted with ethyl acetate. The extract was washed with water, and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) to give the title compound (0.84 g) having the following physical data.

TLC: R<sub>f</sub> 0.37 (ethyl acetate : benzene = 1 : 1);  
 IR(cm<sup>-1</sup>): ν 3401, 3063, 2930, 1586, 1489, 1451, 1351, 1261, 1190, 1150, 1077, 1050, 1011, 969, 903, 822, 757, 697.

## Reference example 6

1-[2-(Tetrahydropyran-2-yl)oxyethoxy]-3-(3-methylsulfonyloxy-4-diphenylaminosulfonylbutyl)benzene

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To a solution of the compound prepared in reference example 5 (0.66 g) in methylene chloride (20 ml) were added successively triethylamine (0.305 g) and methanesulfonyl chloride (0.12 ml) at 0 °C. The mixture was stirred for 10 min at same temperature. After quenched by addition of water and the mixture

EP 0 558 062 A2

was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue containing the title compound having the following physical data. The residue was used for the next reaction without further purification.

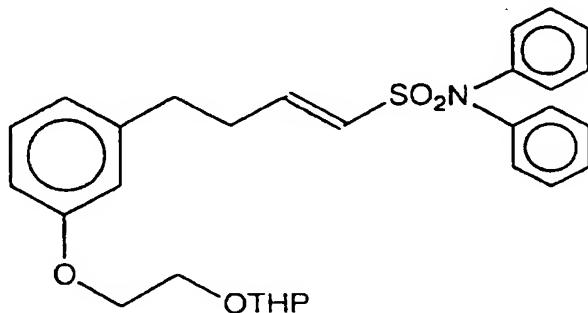
5 TLC: R<sub>f</sub> 0.31 (ethyl acetate : benzene = 1 : 8).

Reference example 7

1-[2-(Tetrahydropyran-2-yl)oxyethoxy]-3-(4-diphenylaminosulfonyl-3-butenyl)benzene

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To a solution of the residue obtained in reference example 6 in benzene was added 1, 8-diazabicyclo[5.4, 0]-7-undecene (0.382 g) at 0 °C. The mixture was stirred for 10 min at 0 °C. After quenched by addition of water and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated to give the title compound (0.63 g) having the following physical data.

30 TLC: R<sub>f</sub> 0.27 (ethyl acetate : benzene = 1 : 8);  
IR (cm<sup>-1</sup>): ν 3063, 2943, 2873, 1734, 1586, 1489, 1451, 1354, 1260, 1152, 1126, 1076, 1034, 989, 969, 904, 874, 816, 757, 697.

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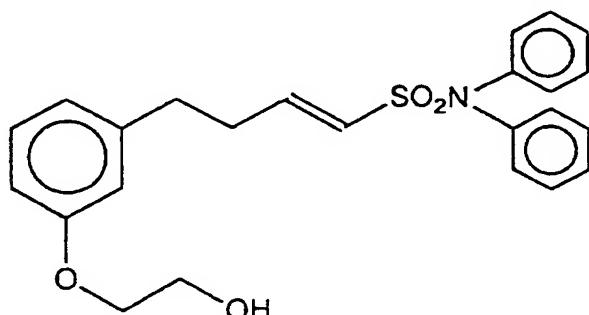
Reference example 8

2-[3-(4-Diphenylaminosulfonyl-3-butenyl)phenoxy]ethanol

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55 To a solution of the compound prepared in reference example 7 (0.541 g) in methanol (20 ml) was added a catalytic amount of 10-camphorsulfonic acid (dl form) at room temperature. The mixture was stirred for 1 h at room temperature. To the reaction mixture was added triethylamine (0.1 ml) and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2 → 1 : 1) to give

the title compound (0.404 g) having the following physical data.

TLC: Rf 0.37 (ethyl acetate : benzene = 1 : 1);

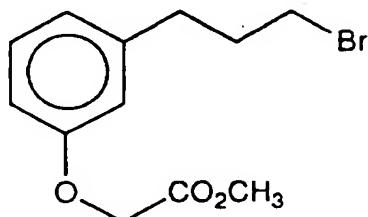
IR(cm<sup>-1</sup>): ν 3401, 3063, 2930, 1586, 1489, 1451, 1351, 1261, 1190, 1150, 1077, 1050, 1011, 969, 903, 822, 757, 697.

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#### Reference example 9

Methyl 3-(3-bromopropyl)phenoxyacetate

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To a stirred solution of methyl 3-(3-hydroxypropyl)phenoxyacetate (2.00 g) in methylene chloride (20 ml) were added successively triphenylphosphine (2.81 g) and tetrabromomethane (3.55 g) at room temperature. The mixture was evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (1.69 g) having the following physical data.

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TLC: Rf 0.26 (n-hexane : ethyl acetate = 2 : 1);

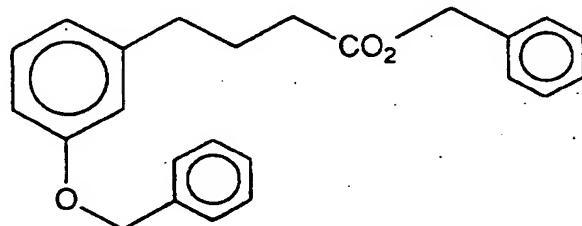
NMR: δ 7.30-7.06 (1H, m), 6.90-6.60 (3H, m), 4.63 (2H, s), 3.81 (3H, s), 3.38 (2H, t, J = 8Hz), 2.76 (2H, t, J = 8Hz), 2.32-1.96 (2H, m).

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#### Reference example 10

1-Benzoyloxy-3-(3-benzyloxycarbonylpropyl)benzene

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A mixture of 1-hydroxy-3-(3-benzyloxycarbonylpropyl)benzene (2.0 g), benzylbromide (1.14 ml), potassium bicarbonate (1.53 g) and dimethylformamide (20 ml) was stirred for 3h at room temperature. The mixture was quenched by addition of water and extracted with a mixture of n-hexane : ethyl acetate (3 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) to give the title compound (2.55 g) having the following physical data.

TLC: Rf 0.33 (n-hexane : ethyl acetate = 7 : 1);

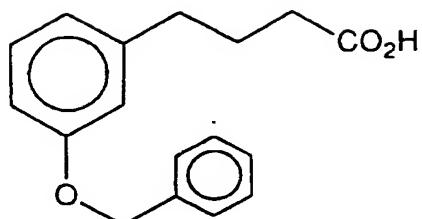
IR(cm<sup>-1</sup>): ν 3065, 3033, 2939, 2866, 1734, 1583, 1489, 1455, 1382, 1315, 1258, 1156, 1082, 1027, 908, 850, 777, 739.

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## Reference example 11

4-(3-Benzylxyphenoxy)butanoic acid

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To a solution of the compound prepared in reference example 10 (2.42 g) in a mixture of tetrahydrofuran-methanol (2 : 1) (20 ml) was added 2N aqueous solution of sodium hydroxide (11 ml) at 0 °C. The mixture was stirred for 3h at room temperature. After neutralized by addition of 2N aqueous 20 solution of hydrochloric acid and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from n-hexane-ethyl acetate to give the title compound (1.5 g) having the following physical data.

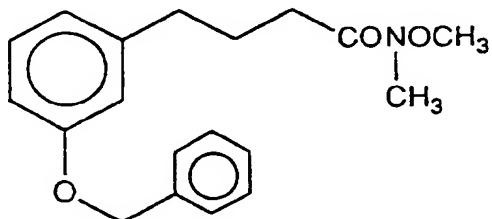
mp.: 100.0-102.0 °C;  
 TLC: R<sub>f</sub> 0.53 (ethyl acetate);  
 NMR: δ 7.50-7.08 (7H, m), 6.93-6.70 (3H, m), 5.04 (2H, s), 2.66 (2H, t, J = 7Hz), 2.36 (2H, t, J = 8Hz), 2.16-1.93 (2H, m).

## Reference example 12

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1-Benzylxy-3-[3-(N-methyl-N-methoxyamino)carbonylpropyl]benzene

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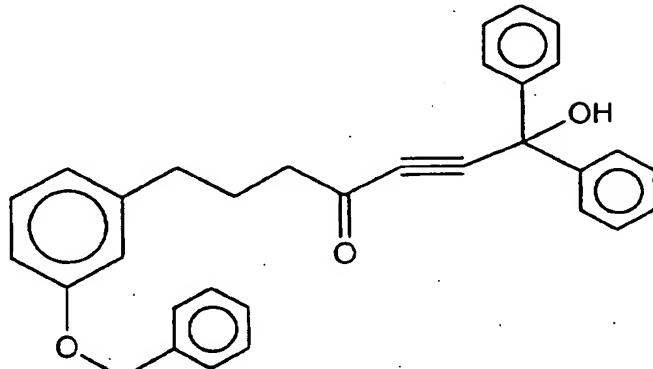
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An ethyl chloroformate (0.96 ml) was dissolved with stirring solution of a compound prepared in reference example 11 (2.45 g) and triethylamine (1.35 ml) in methylene chloride (30 ml) at -10 °C. After stirred for 10 min at room temperature, to the mixture were added successively triethylamine (2.8 ml) and N-methyl-N-methoxyamine hydrochloride (980 mg) at -10 °C. The mixture was further stirred for 1h at room temperature, and was poured into water. The mixture was extracted with a mixture of n-hexane-ethyl acetate (1 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) to give the title compound (2.67 g) having the following physical data.

TLC: R<sub>f</sub> 0.23 (n-hexane : ethyl acetate = 2 : 1);  
 NMR: δ 7.48-7.03 (6H, m), 6.86-6.67 (3H, m), 5.04 (2H, s), 3.61 (3H, s), 3.16 (3H, s), 2.78-2.30 (4H, m), 2.12-1.80 (2H, m).

## Reference example 13

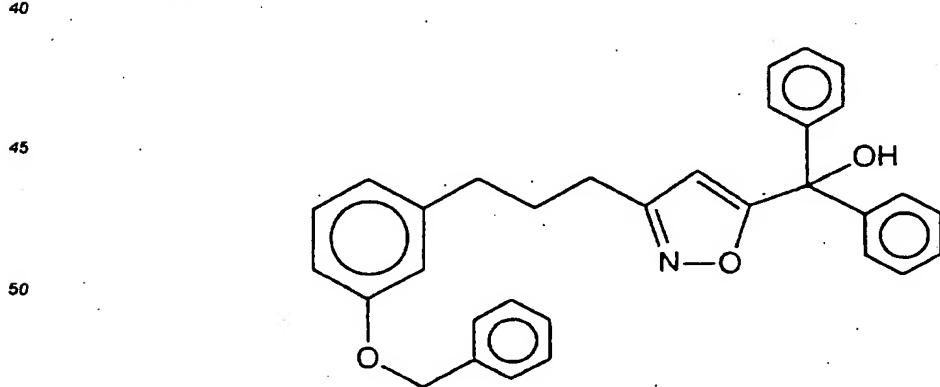
1-Benzyloxy-3-(3-hydroxy-3,3-diphenyl-1-propynyl)carbonylpropyl benzene



To a solution 1,1-diphenyl-2-propyn-1-ol (3.89 g) in tetrahydrofuran (40 ml) was added n-butyllithium (23.4 ml of 1.6M in n-hexane) at -78 °C. After stirred for 30 min at same temperature, to the mixture was added boron trifluoride etherate (5.05 ml). The mixture was stirred for 30 min at -78 °C. To the mixture, the compound prepared in reference example 12 (2.67 g) in tetrahydrofuran (20 ml) was added at same temperature. After stirred for 1h at -78 °C, the reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, and the mixture stirred for 30 min at room temperature. The mixture was extracted with a mixture of n-hexane-ethyl acetate (3 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (2.8 g) having the following physical data.  
 mp.: 54.5 - 56.0 °C  
 TLC: R<sub>f</sub> 0.18 (n-hexane : ethyl acetate = 6 : 1);  
 NMR: δ 7.45-7.10 (16H, m), 6.86-6.71 (3H, m), 5.01 (2H, s), 3.00 (1H, s), 2.68-2.53 (4H, m), 2.10-1.90 (2H, m).

## Reference example 14

1-Benzyl-3-[3-(5-hydroxydiphenylmethylisoxazole-3-yl)propyl] benzene



A mixture of the compound prepared in reference example 13 (1.0 g), hydroxylamine hydrochloride (1.5 g), pyridine (10 ml) and ethanol (10 ml) was refluxed for 6h. The mixture was concentrated under reduced

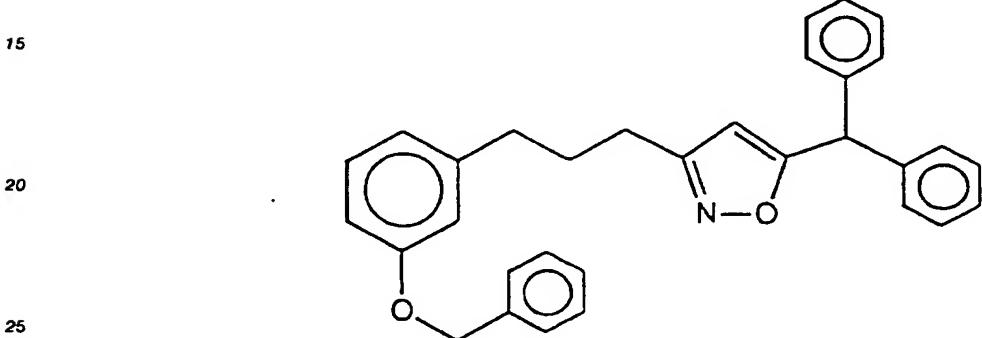
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pressure, the residue was quenched by addition of water. The mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (940 mg) having the following physical data

- 5 mp.: 89.0 - 90.5 °C;  
NMR: δ 7.43-7.16 (16H, m), 6.80-6.74 (3H, m), 5.80 (1H, s), 5.03 (2H, s), 3.17 (1H, s), 2.67-2.61 (4H, m),  
2.00-1.90 (2H, m).

Reference example 15

- 10 1-Benzylxoy-3-[3-(5-diphenylmethylisoxazol-3-yl)propyl]benzene



To a solution of the compound prepared in reference example 14 (860 mg) in trifluoroacetic acid (8.0 ml) was added a solution triethylsilane (440 mg) in methylene chloride (2.0 ml) with stirring at 0 °C. After stirred for 30 min at room temperature, the mixture was concentrated under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 8 : 1) to give the title compound (640 mg) having the following physical data.

- 35 TLC: Rf 0.50 (n-hexane : ethyl acetate = 3 : 1);  
NMR: δ 7.50-7.00 (16H, m), 6.85-6.65 (3H, m), 5.70 (1H, s), 5.30 (1H, s), 5.03 (2H, s), 2.80-2.50 (4H, m),  
2.17-1.75 (2H, m).

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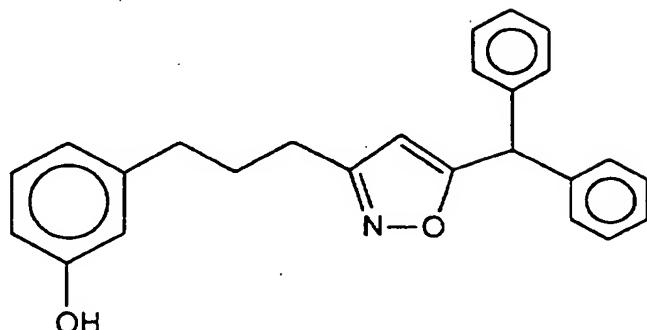
## Reference example 16

1-Hydroxy-3-[3-(5-diphenylmethylisoxazol-3-yl)propyl]benzene

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20 To a solution of the compound prepared in reference example 15 (550 mg) in methylene chloride (6.0 ml) was added boron tribromide (0.34 ml) with stirring at 0 °C. The mixture was stirred for 30 min at 0 °C, and poured into ice water and extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1  
 25 → 3 : 1) to give the title compound (376 mg) having the following physical data.  
 mp.: 114.5 - 117 °C;  
 TLC: R<sub>f</sub> 0.22 (n-hexane : ethyl acetate = 3 : 1);  
 NMR: δ 7.39-7.05 (11H, m), 6.75-6.60(3H, m), 5.73 (1H, s), 5.62-5.53 (1H, m), 5.52 (1H, s), 2.70-2.52 (4H, m), 2.02-1.84 (2H, m).

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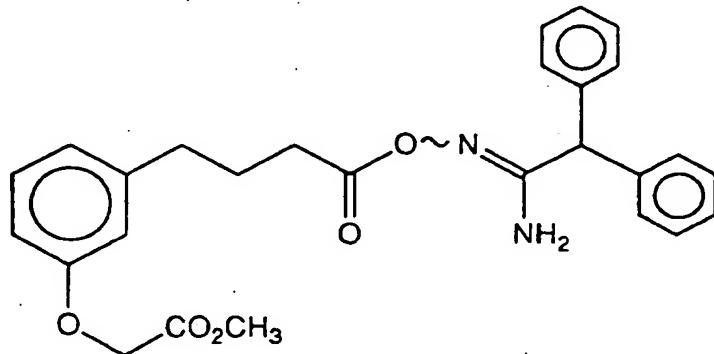
## Reference example 17

Methyl 3-[3-[(1-amino-2, 2-diphenylethyldene)aminoxy carbonyl] propyl]phenoxyacetate

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A suspension of 4-(3-methoxycarbonylmethoxyphenyl)butanoic acid (289 mg) and thionyl chloride (5.0 ml) was refluxed for 1 h. The mixture was cooled to room temperature and concentrated under reduced pressure. To a suspension of the residue and 1,1-diphenyl-2-amino-2-hydroxyiminoethane (285 mg) in  
 55 methylene chloride (5 ml) was added diethylamine (0.32 ml) with stirring at room temperature. The mixture was stirred overnight at room temperature. After quenched by addition of water, the mixture was extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica

gel flash chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (193 mg) having the following physical data.

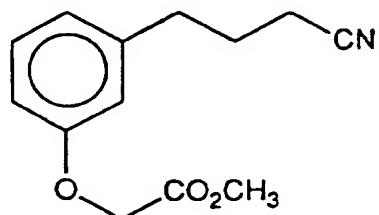
NMR:  $\delta$  7.40-7.00 (11H, m), 6.90-6.50 (3H, m), 5.26 (1H, s), 4.75 (2H, brs), 4.58 (2H, s), 3.78 (3H, s), 2.64 (2H, t, J = 7Hz), 2.40 (2H, t, J = 7Hz), 2.00 (2H, m); MS (m/z): 461 ( $M^+ + 1$ ).

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#### Reference example 18

Methyl 3-(3-cyanopropyl)phenoxyacetate

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A mixture of potassium cyanide (1.16 g), 18-crown-6 (236 mg) and acetonitrile (18 ml) was stirred for 15 min under an atmosphere of argon. A mixture of methyl 3-(3-hydroxypropyl)phenoxyacetate (2.0 g) and tributylphosphine (1.99 g) in acetonitrile (10 ml) was added to the reaction mixture, followed by the dropwise addition of a solution of carbon tetrachloride (0.95 ml) in acetonitrile (10 ml) with cooling in ice bath. The mixture was stirred overnight at room temperature. The mixture was diluted with ether, and washed with aqueous 10% citric acid. After the addition of carbon tetrachloride (10 ml), the mixture was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 9 : 1) to give the title compound (1.47 g) having the following physical data.

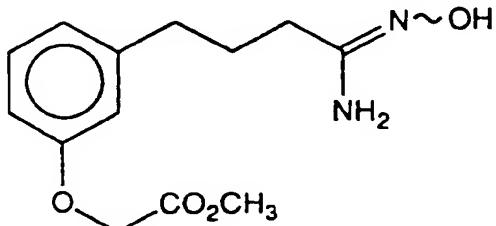
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NMR:  $\delta$  7.20 (1H, t, J = 7Hz), 6.90-6.60 (3H, m), 4.60 (2H, s), 3.80 (3H, s), 2.74 (2H, t, J = 7Hz), 2.30(2H, t, J = 7 Hz), 1 .98(2H, m).

#### Reference example 19

35 Methyl 3-(4-amino-4-hydroxyiminobutyl)phenoxyacetate

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To a mixture of ethanol-water (5:1) (30 ml) were added successively the compound prepared in reference example 18 (1.01 g), hydroxyamine hydrochloride (331 mg) and sodium acetate (391 mg). The mixture was refluxed overnight. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (150 mg) having the following physical data.

NMR:  $\delta$  7.13 (1H, t, J = 7 Hz), 6.90-6.50 (3H, m), 5.10 (3H, brs), 4.60 (2H, s), 3.80 (3H, s), 2.63 (2H, t, J = 7 Hz), 2.37 (2H, t, J = 7 Hz), 1.95 (2H, m)

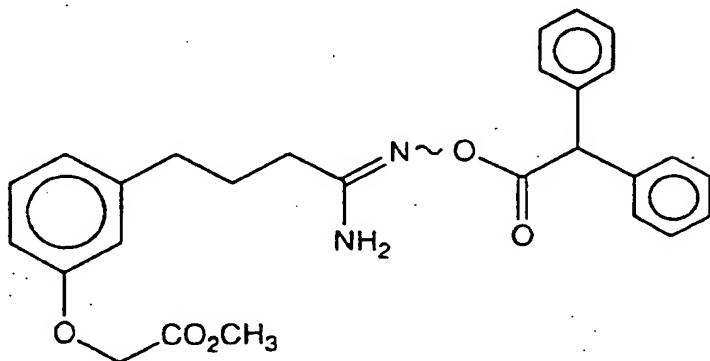
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## Reference example 20

Methyl 3-(4-amino-4-diphenylmethylcarbonyloxyiminobutyl)phenoxy acetate

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A suspension of diphenylacetic acid (252 mg) and thionyl chloride (5.0 ml) was refluxed for 1h. The mixture was cooled to room temperature and concentrated under reduced pressure. To a solution of the residue and the compound prepared in reference example 19 (144 mg) in methylene chloride (5.0 ml) was added triethylamine (0.33 ml) at room temperature. The mixture was stirred overnight at room temperature, quenched by addition of water, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel flash chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (61 mg) having the following physical data.

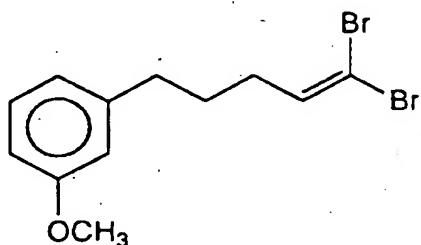
NMR:  $\delta$  7.40-7.00 (11H, m), 6.90-6.50 (3H, m), 5.10 (1H, s), 4.58 (2H, s), 3.79 (3H, s), 2.60 (2H, m), 2.21 (2H, m), 1.90 (2H, m);  
 MS (m/z): 461 ( $M^+ + 1$ )

## Reference example 21

35 1-(5,5-Dibromo-4-pentenyl)-3-methoxybenzene

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To a solution of carbon tetrabromide (16.7 g) in methylene chloride (35 ml) was added triphenylphosphine (26.0 g) in methylene chloride (35 ml) at 0°C, and the mixture was stirred for 10 min. To the mixture was added a solution of 1-(3-formylpropyl)-3-methoxybenzene (3.00 g) in methylene chloride (20 ml) at 0°C. The mixture was stirred for 30 min at 0°C. To the mixture was gradually added n-hexane, and filtrated to remove triphenylphosphineoxide. The filtrate was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 24 : 1) to give the title compound (5.33 g) having the following physical data.

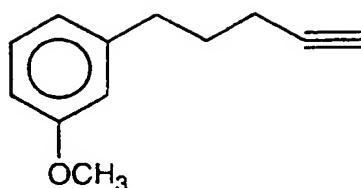
MS (m/z): 334 ( $M^+$ ).

TLC: Rf 0.34 (n-hexane : ethyl acetate = 24 : 1).

## Reference example 22

1-(4-pentynyl)-3-methoxybenzene

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To a solution of the compound prepared in reference example 21 (3.58 g) in THF (40 ml) was added dropwise n-butyllithium (14.7 ml; 1.6M/L in hexane solution) at -70 °C. The mixture was stirred for 30 min at -70 °C. After quenched by addition of water and aqueous solution of ammonium chloride at the same temperature, the mixture was warmed up to room temperature. The mixture was extracted with n-hexane - ethyl acetate (6 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 24 : 1) to give the title compound (1.86 g) having the following physical data.

TLC: R<sub>f</sub> 0.32 (n-hexane : ethyl acetate = 24 : 1);  
 IR(cm<sup>-1</sup>): ν 3295, 2943, 2117, 1602, 1489, 1261.

## Reference example 23

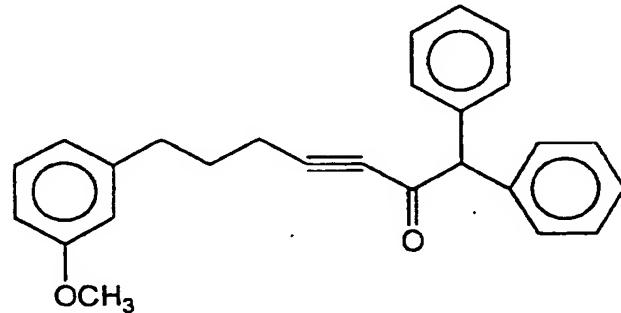
1-(7,7-Diphenyl-6-oxo-4-heptynyl)-3-methoxybenzene

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55 To a mixture of ethylmagnesium bromide (3.4 ml; 3.0 M/L in ether solution) and THF (20 ml) was added dropwise a solution of the compound prepared in reference example 22 (1.5 g) in THF (15 ml) over a 10 min period. The mixture was stirred for 2h at room temperature. To the mixture was added a solution of diphenylacetaldehyde (1.7 g) in THF (10 ml). The mixture was stirred for 2h. After quenched by addition of ammonium chloride, the mixture was extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. To a solution of the residue in ether (40 ml) was added manganese (IV) oxide (2.0 g) at room temperature. The mixture was stirred for 2h. The mixture was filtrated, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (1.99 g) having the following physical data.

MS (m/z): 368 (M<sup>+</sup>).TLC: R<sub>f</sub> 0.46 (n-hexane : ethyl acetate = 3 : 1).

## Reference example 24

1-(6-Imino-4-hydroxy-7,7-diphenyl-4-heptynyl)-3-methoxybenzene

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A mixture of the compound (400 mg) prepared by the same procedure as reference example 14 using the compound prepared in reference example 23, Raney nickel (300 mg; registered trade mark) and ethanol (5 ml) was stirred overnight under an atmosphere of hydrogen. The mixture was filtered through Celite (registered trade mark), and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : benzene = 7 : 93) to give the title compound (184 mg) having the following physical data.  
 MS (m/z): 385 (M<sup>+</sup>).  
 TLC: Rf 0.26 (n-hexane : ethyl acetate = 3 : 1).

## Reference example 25

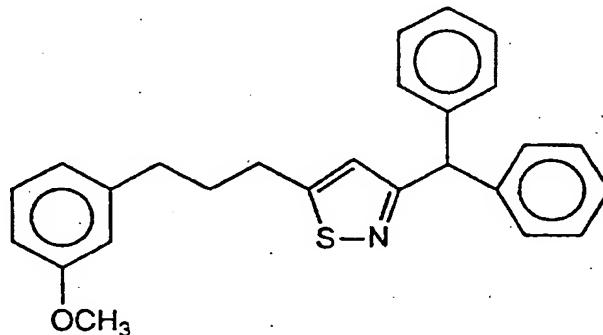
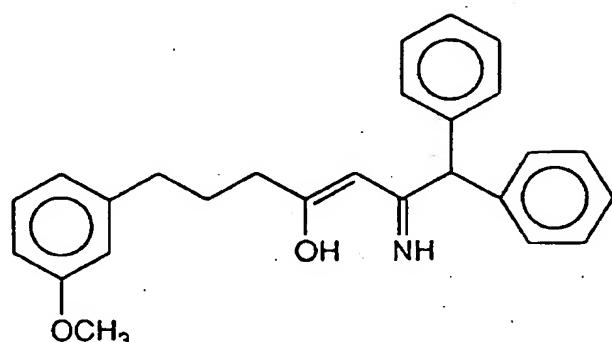
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1-[3-(3-Diphenylmethylisothiazol-5-yl)propyl]-3-methoxybenzene

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A mixture of the compound prepared in reference example 24 (121 mg), p-chloranil (77 mg), phosphorus pentasulfide (209 mg) and toluene (2 ml) was refluxed for 30 min. After cooled to room temperature, to the mixture was added benzene. The mixture was filtrated, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 6 : 1) to give the title compound (62 mg) having the following physical data.  
 MS (m/z): 399 (M<sup>+</sup>).  
 TLC: Rf 0.30 (n-hexane : ethyl acetate = 6 : 1).

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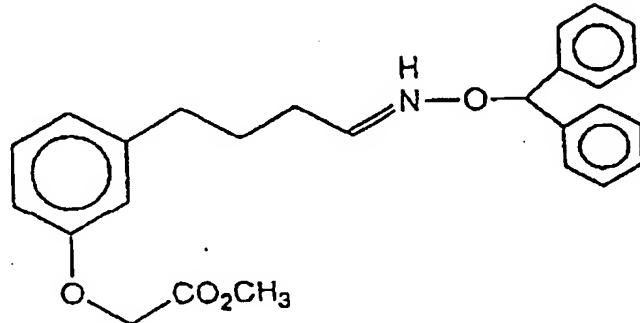
## Example 1

Methyl 3-(4-diphenylmethoxyiminobutyl)phenoxyacetate

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20 To a solution of the compound prepared in reference example 1 (300 mg) in ethanol (10 ml) was added diphenylmethoxyamine (253 mg) at room temperature. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (benzene : ethyl acetate = 9 : 1) to give the title compound (520 mg) having the following physical data.

25 TLC: R<sub>f</sub> 0.31 (n-hexane : ethyl acetate = 4 : 1);

NMR: δ 7.60-7.10 (12H, m), 6.90-6.80 (3H, m), 6.22 (1H, s), 4.60 (2H, s), 3.79 (3H, s), 2.80-2.00 (4H, m), 1.80 (2H, m).

## Example 2

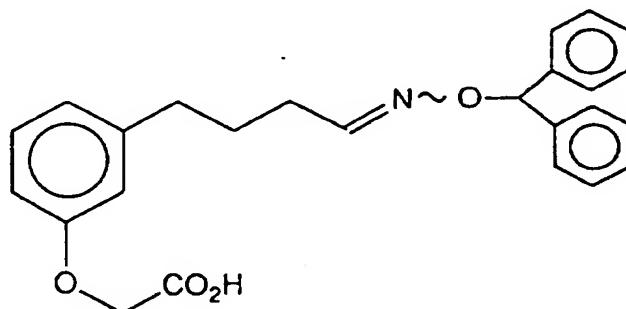
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3-(4-Diphenylmethoxyiminobutyl)phenoxyacetic acid

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To a solution of the compound prepared in example 1 (305 mg) in a mixture of dimethoxymethane (3.0 ml) and methanol (1.0 ml) was added 2N aqueous solution of sodium hydroxide (0.5 ml) at room temperature. After stirred for 1h, the mixture was quenched by addition of 1N hydrochloric acid (0.5 ml), and extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1) to give the title compound (277 mg) having the following physical data.

MS (m/z): 403 (M<sup>+</sup>), 381, 359, 345, 236, 219, 184, 168;

NMR: δ 7.55 (1H, t, J=6 Hz), 7.40-7.10 (11H, m), 6.90-6.80 (3H, m), 6.20 (1H, s), 4.62 (2H, s), 2.80-2.40 (3H, m), 2.17 (1H, brs), 1.80 (2H, m).

Example 2(a)-2(c)

By the same procedure as in example 2, using the compound prepared in the same procedure as in reference example 1 → example 1 which was using corresponding phenoxyacetic acid derivative compound instead of methyl 3-(4-hydroxybutyl) phenoxyacetate, compounds having the following physical data shown in the table 3 were given

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Ex. No.	Structure of the example compound	MS ( $m/z$ )	IR ( $\text{cm}^{-1}$ )
2 (a)		389( $M^+$ ), 344, 222, 205, 184, 168	[KBr method] $\nu$ 3030, 2911, 1743, 1708, 1610, 1515, 1455, 1431, 1237, 1189, 1095, 1024, 919, 832, 746, 705
2 (b)		403( $M^+$ ), 360, 345, 236, 219, 184, 118, 152	$\nu$ 3030, 2927, 1736, 1611, 1586, 1510, 1454, 1301, 1218, 1180, 1081, 1022, 920, 830, 740, 702, 609
2 (c)		390 ( $M^+ + 1$ )	$\nu$ 3031, 2922, 1734, 1685, 1494, 1454, 1241, 1160, 1084, 1020, 919, 741, 700

Table 3

The example compounds shown in the table 3 are named as follows:

- 2(a) 4-(3-Diphenylmethoxyiminopropyl)phenoxyacetic acid,  
 2(b) 4-(4-Diphenylmethoxyiminobutyl)phenoxyacetic acid,  
 2(c) 3-(3-Diphenylmethoxyiminopropyl)phenoxyacetic acid,

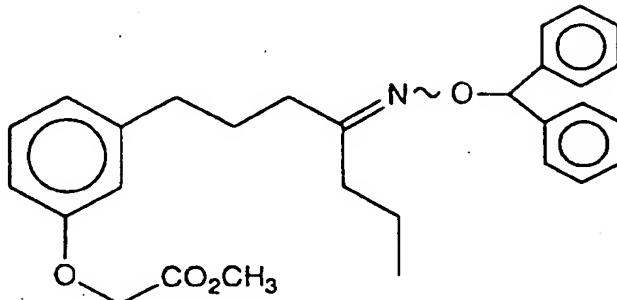
## Example 3

Methyl 3-(4-diphenylmethoxyiminoheptyl)phenoxyacetate

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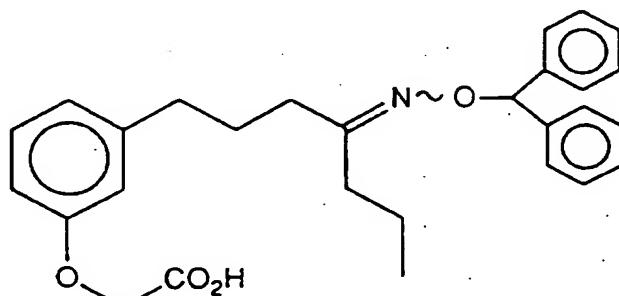
## 25 Example 4

3-(4-Diphenylmethoxyiminoheptyl)phenoxyacetic acid

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By the same procedure as in example 1, using the compound prepared in reference example 3, the title compound having the following physical data was given.

45 TLC: Rf 0.35 (n-hexane : ethyl acetate = 3 : 1);

IR (cm<sup>-1</sup>): > 3062, 3030, 2958, 2872, 1763, 1741, 1586, 1494, 1452, 1377, 1289, 1209, 1159, 1088, 1025,

937, 744, 700.

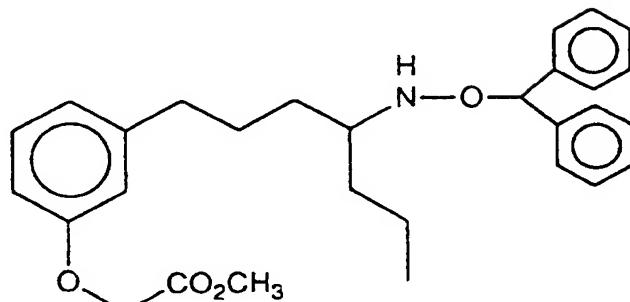
## Example 5

Methyl 3-(4-diphenylmethoxyaminoheptyl)phenoxyacetate

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To a solution of the compound prepared in example 3 (150 mg) in methanol (1 ml) was added sodium cyanoborohydride (82 mg) at room temperature. This solution was adjusted to pH 3 by addition of a saturated hydrochloride in methanol and this mixture was stirred for 2h at room temperature. After neutralized by addition of a saturated aqueous solution of sodium bicarbonate, the mixture was extracted with ethyl acetate. The extract was washed with water and aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1) to give title compound (147 mg) having the following physical data.

TLC: R<sub>f</sub> 0.34 (n-hexane : ethyl acetate = 3 : 1);  
 IR (cm<sup>-1</sup>): ν 3030, 2932, 2869, 1764, 1741, 1586, 1493, 1452, 1376, 1209, 1159, 1086, 1029, 888, 761, 743, 699.

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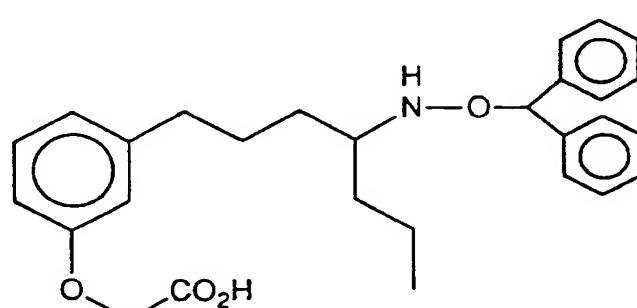
## Example 6

3-(4-Diphenylmethoxyaminoheptyl)phenoxyacetic acid

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By the same procedure as example 2, using the compound prepared in example 5 (125 mg), the title compound (115 mg) having the following physical data was given  
 TLC: R<sub>f</sub> 0.21 (chloroform : methanol = 4 : 1);  
 IR (cm<sup>-1</sup>): ν 3031, 2932, 2871, 1738, 1586, 1494, 1454, 1374, 1241, 1159, 1082, 1046, 915, 762, 744, 698.

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Example 7

Methyl 3-(3,3-diphenylmethylpropyl)aminocarbonylmethylphenoxy acetate

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A mixture of 3-methoxycarbonylmethoxyphenylacetic acid (150 mg), 2-chloro-N-methylpyridinium iodide (241 mg), 3,3-diphenylpropylamine (146 mg) and triethylamine (0.26 ml) in methylene chloride (7 ml) was stirred overnight at room temperature. The mixture was poured into 1N hydrochloric acid, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 25) to give title compound (125 mg) having the following physical data.

TLC: R<sub>f</sub> 0.33 (ethyl acetate : methylene chloride = 1 : 9);

NMR: δ 7.40-7.00 (11H, m), 6.90-6.70 (3H, m), 5.30 (1H, m), 4.63 (2H, s), 3.83 (1H, t, J = 7Hz), 3.80 (3H, s),

35 3.47 (2H, s), 3.17 (2H, dt, J = 8, 7Hz), 2.20 (2H, dt, J = 5, 7Hz).

Example 8

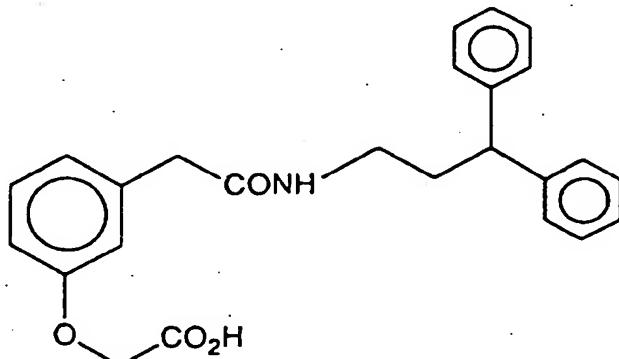
3-(3,3-diphenylpropyl)aminocarbonylmethylphenoxyacetic acid

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By the same procedure as example 2, using the compound prepared in example 7 (119 mg), the title compound (98 mg) having the following physical data was given.

55 TLC: R<sub>f</sub> 0.48 (methylene chloride : methanol = 10 : 3);

IR (cm<sup>-1</sup>): ν 3295, 3024, 2880, 2526, 1757, 1584, 1557, 1490, 1469, 1450, 1381, 1356, 1304, 1285, 1242, 1204, 1155, 1087, 1030, 958, 905, 880, 776, 753, 741, 697, 674, 638, 614, 588, 557, 482, 456, 431.

## Example 8(a) - 8(cc)

By the same procedure as in example 7 → example 2, using corresponding phenoxyacetic acid derivative compound and corresponding amine, compounds having the following physical data shown in the table 4 were given

EX. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
8 (a)		Rf 0.50 (ethylene chloride : methanol = 10:3)	$\nu$ 3033. 1742. 1614. 1587. 1495. 1438. 1213. 1159. 1062. 1017. 780. 732. 702
8 (b)		Rf 0.53 (ethylene chloride : methanol = 10:3)	$\nu$ 3436. 3031. 1742. 1603. 1494. 1452. 1363. 1221. 1160. 1083. 1029. 954. 775. 736. 700
8 (c)		Rf 0.30 (ethylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3268. 3037. 1724. 1636. 1588. 1561. 1452. 1453. 1432. 1400. 1358. 1348. 1314. 1243. 1259. 1231. 1172. 1158. 1093. 1080. 1026. 951. 919. 855. 787. 766. 744. 696. 618. 605. 557. 532. 489

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Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
8 (d)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3297, 3058, 2917, 1719, 1703, 1653, 1613, 1589, 1531, 1491, 1451, 1434, 1412, 1359, 1341, 1277, 1231, 1161, 1065, 1032, 978, 752, 742, 702, 642, 620
8 (e)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3273, 3038, 2916, 1753, 1674, 1590, 1516, 1494, 1460, 1431, 1315, 1276, 1241, 1163, 1098, 1065, 1030, 965, 877, 784, 752, 693, 626, 546, 507
8 (f)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3318, 3063, 2921, 1752, 1646, 1586, 1516, 1495, 1440, 1255, 1165, 1100, 1028, 966, 914, 877, 760, 701, 541

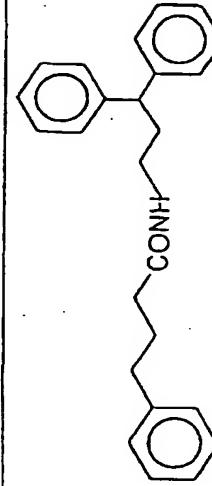
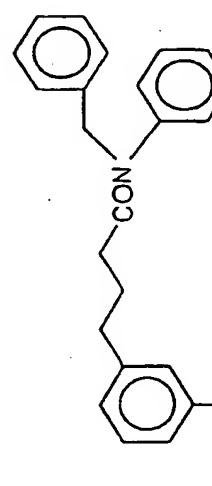
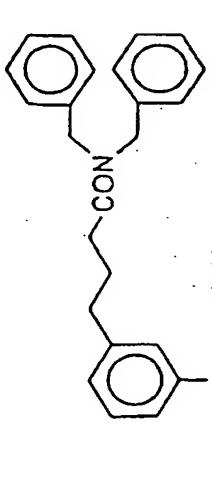
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Table 4 (continued)

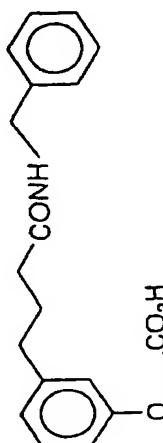
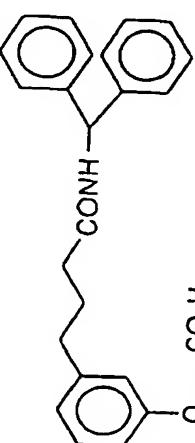
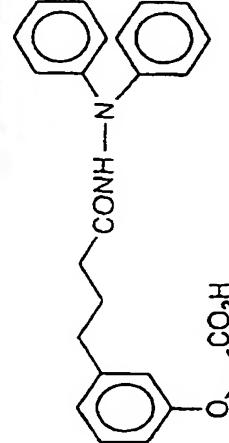
Ex. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
8 (g)		Rf 0.40 [KBr method] ν 3309. 3028. 2912. 1721. 1625. 1604. 1580. 1494. 1435. 1299. 1246. 1160. 1087. 1013. 924. 886. 774. 756. 742. 704. 633. 585. 542	
8 (h)		Rf 0.38 [KBr method] ν 3233. 3032. 2912. 1719. 1641. 1609. 1588. 1532. 1494. 1458. 1436. 1341. 1300. 1250. 1161. 1098. 1086. 1051. 985. 914. 835. 813. 764. 748. 698. 602. 574. 531	
8 (i)		Rf 0.40 [KBr method] ν 3314. 3057. 1737. 1639. 1587. 1511. 1490. 1446. 1367. 1324. 1304. 1221. 1158. 1075. 1028. 1000. 972. 918. 879. 774. 695. 651. 628. 549. 452	

Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
8 (j)		Rf 0.50 (methylene chloride : methanol = 10:3)	$\nu$ 3351, 3027, 2933, 1734, 1713, 1603, 1558, 1491, 1452, 1364, 1227, 1160, 1080, 1031, 914, 776, 752, 701
8 (k)		Rf 0.53 (methylene chloride : methanol = 10:3)	$\nu$ 3033, 2930, 1742, 1611, 1586, 1495, 1453, 1413, 1357, 1267, 1208, 1158, 1079, 1017, 878, 777, 700
8 (l)		Rf 0.53 (methylene chloride : methanol = 10:3)	$\nu$ 3031, 2927, 1746, 1604, 1495, 1452, 1361, 1220, 1160, 1083, 1029, 953, 879, 183, 735, 699

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Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
8 (m)		Rf 0.33 (methylenecloride : methanol = 10:3)	[KBr method] $\nu$ 3320, 3031, 2952, 2587, 1737, 1641, 1611, 1580, 1541, 1465, 1461, 1423, 1377, 1349, 1297, 1279, 1239, 1165, 1103, 1030, 1009, 925, 877, 781, 770, 735, 695
8 (n)		Rf 0.50 (methylenecloride : methanol = 10:3)	[KBr method] $\nu$ 3320, 3034, 2948, 1750, 1644, 1586, 1532, 1495, 1459, 1426, 1377, 1304, 1258, 1243, 1212, 1164, 1100, 1032, 935, 873, 756, 698, 644, 605
8 (o)		Rf 0.56 (methylenecloride : methanol = 10:3)	[KBr method] $\nu$ 3279, 3027, 2932, 2587, 1744, 1669, 1591, 1518, 1495, 1430, 1383, 1329, 1256, 1236, 1174, 1094, 1031, 939, 923, 853, 782, 746, 698, 631, 559

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Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
B (p)		Rf 0.45 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3344, 3031, 2944, 1746, 1640, 1603, 1523, 1495, 1454, 1419, 1244, 1168, 1090, 1031, 902, 785, 781, 702, 642, 584, 538
B (q)		Rf 0.47 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3347, 2938, 2866, 2549, 1737, 1615, 1587, 1553, 1493, 1452, 1437, 1362, 1293, 1226, 1158, 1083, 1028, 908, 877, 790, 753, 704, 630, 587, 543
B (r)		Rf 0.44 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3205, 2930, 1736, 1655, 1586, 1491, 1452, 1229, 1160, 1082, 1023, 875, 762, 746, 698

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Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR (cm <sup>-1</sup> )
8 (s)		Rf 0.50 [KBr method]  (methylene chloride : methanol = 10:3)	$\nu$ 3182, 3159, 3053, 2965, 2905, 2759, 2524, 1746, 1631, 1564, 1489, 1457, 1432, 1391, 1359, 1322, 1309, 1272, 1229, 1156, 1087, 1028, 956, 927, 813, 774, 741, 695, 637, 600, 523, 463, 431
8 ((1))		Rf 0.32 [KBr method]  (methylene chloride : methanol = 10:3)	$\nu$ 3326, 3023, 2920, 2880, 1719, 1585, 1494, 1484, 1451, 1435, 1378, 1312, 1293, 1249, 1208, 1168, 1091, 894, 865, 785, 770, 750, 696, 606, 585, 495, 468
8 (u)		Rf 0.49 [KBr method]  (methylene chloride : methanol = 10:3)	$\nu$ 3031, 2931, 1746, 1613, 1587, 1495, 1454, 1416, 1260, 1211, 1159, 1082, 1018, 863, 778, 756, 700

Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR (cm <sup>-1</sup> )
8 (v)		Rf 0.53 (methylene chloride : methanol = 10:3)	$\nu$ 3030, 2921, 1746, 1603, 1491, 1452, 1361, 1217, 1161, 1082, 1029, 1002, 956, 883, 752, 699
8 (w)		Rf 0.21 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3347, 3293, 3033, 2935, 1742, 1712, 1640, 1610, 1537, 1547, 1492, 1454, 1432, 1350, 1301, 1291, 1213, 1159, 1104, 1080, 1020, 922, 887, 781, 749, 695, 498, 456
8 (x)		Rf 0.43 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3326, 3061, 1732, 1651, 1614, 1585, 1535, 1496, 1455, 1427, 1381, 1259, 1246, 1220, 1166, 1106, 980, 922, 874, 789, 769, 745, 697, 610, 532

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Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR (cm <sup>-1</sup> )
8 (y)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3279, 1737, 1704, 1613, 1589, 1523, 1496, 1453, 1414, 1391, 1286, 1234, 1160, 1086, 921, 771, 747, 693, 630, 507
8 (z)		Rf 0.38 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3326, 3063, 2916, 2582, 1752, 1641, 1595, 1537, 1495, 1455, 1432, 1319, 1300, 1251, 1175, 1094, 1030, 913, 847, 790, 759, 699, 644, 539, 508
8 (aa)		Rf 0.50 (methylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3339, 3060, 2931, 1737, 1603, 1561, 1451, 1452, 1224, 1159, 1087, 1032, 1008, 961, 783, 755, 742, 701, 586, 540

Table 4 (continued)

Ex. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
8 (b)		Rf 0.33 (ethylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3209, 3032, 1736, 1656, 1491, 1452, 1229, 1161, 1084, 1002, 876, 762, 746, 699
8 (cc)		Rf 0.48 (ethylene chloride : methanol = 10:3)	[KBr method] $\nu$ 3181, 3070, 2924, 2524, 1736, 1631, 1584, 1490, 1460, 1440, 1397, 1335, 1313, 1284, 1265, 1232, 1159, 1113, 1094, 1030, 958, 929, 912, 881, 783, 772, 736, 691, 637, 612, 597, 545, 470, 443

The example compounds shown in the table 4 are named as follows:  
 8(a) 3-(N-Benzyl-N-phenylaminocarbonylmethyl)phenoxyacetic acid,  
 8(b) 3-(N,N-Dibenzylaminocarbonylmethyl)phenoxyacetic acid,  
 8(c) 3-(N-Benzylaminocarbonylmethyl)phenoxyacetic acid,  
 8(d) 3-(Diphenylmethylaminocarbonylmethyl)phenoxyacetic acid,

- 8(e) 3-[(N,N-Diphenylamino)aminocarbonylmethyl]phenoxyacetic acid,  
 8(f) 3-(1,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,  
 8(g) 3-(2,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,  
 8(h) 3-(Diphenylmethoxyaminocarbonylmethyl)phenoxyacetic acid,  
 8(i) 3-[(1,1-Diphenylmethylideneamino)aminocarbonylmethyl]phenoxyacetic acid,  
 8(j) 3-[3-(3,3-Diphenylpropylaminocarbonyl)propyl]phenoxyacetic acid,  
 8(k) 3-[3-(N-Benzyl-N-phenylaminocarbonyl)propyl]phenoxyacetic acid,  
 8(l) 3-[3-(N,N-Dibenzylaminocarbonyl)propyl]phenoxyacetic acid.  
 8(m) 3-(3-Benzylaminocarbonylpropyl)phenoxyacetic acid,  
 8(n) 3-(3-Diphenylmethylaminocarbonylpropyl)phenoxyacetic acid,  
 8(o) 3-[3-[(N,N-Diphenylamino)aminocarbonyl]propyl]phenoxyacetic acid,  
 8(p) 3-[3-(1,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,  
 8(q) 3-[3-(2,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,  
 8(r) 3-(3-Diphenylmethoxyaminocarbonylpropyl)phenoxyacetic acid,  
 8(s) 3-[3-[(1,1-Diphenylmethylideneamino)aminocarbonyl]propyl]phenoxyacetic acid,  
 8(t) 3-[2-(3,3-Diphenylpropylaminocarbonyl)ethyl]phenoxyacetic acid,  
 8(u) 3-[2-(N-Benzyl-N-phenylaminocarbonyl)ethyl]phenoxyacetic acid,  
 8(v) 3-[2-(N,N-Dibenzylaminocarbonyl)ethyl]phenoxyacetic acid,  
 8(w) 3-(2-Benzylaminocarbonylethyl)phenoxyacetic acid,  
 8(x) 3-(2-Diphenylmethylaminocarbonylethyl)phenoxyacetic acid,  
 8(y) 3-[2-[(N,N-Diphenylamino)aminocarbonyl]ethyl]phenoxyacetic acid,  
 8(z) 3-[2-(1,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,  
 8(aa) 3-(2-(2,2-Diphenylethylaminocarbonyl)ethyl)phenoxyacetic acid,  
 8(bb) 3-(2-Diphenylmethoxyaminocarbonylethyl)phenoxyacetic acid,  
 8(cc) 3-[2-[(1,1-Diphenylmethylideneamino)aminocarbonyl]ethyl]phenoxyacetic acid,

## Example 9

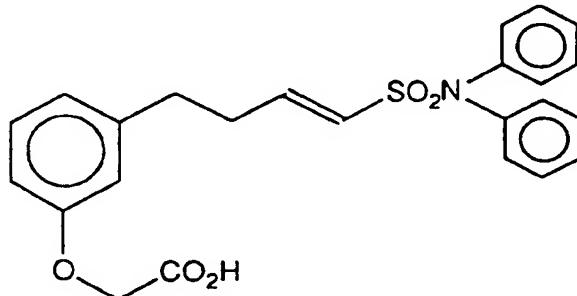
3-(4-Diphenylaminosulfonyl-3-butenyl)phenoxyacetic acid

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To a solution of the compound (0.08 g) prepared by the same procedure as in reference example 1, using the compound prepared in reference example 8, in acetone (2.0 ml) was added 8N Jone's reagent (0.1 ml) at 0 °C. After stirred for 10 min at 0 °C, the mixture was added isopropyl alcohol (0.5 ml). The mixture was stirred for 10 min, added water, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride → methylene chloride : methanol = 40 : 1) to give the title compound (0.035 g) having the following physical data.

TLC: Rf 0.18 (methylene chloride : methanol = 5 : 1);

55 IR [KBr tablet method] ( $\text{cm}^{-1}$ ):  $\nu$  3435, 3051, 2928, 1749, 1714, 1611, 1586, 1489, 1452, 1424, 1353, 1262, 1224, 1193, 1164, 1147, 1091, 1027, 1011, 975, 912, 865, 824, 781, 757, 694, 631, 596, 547.

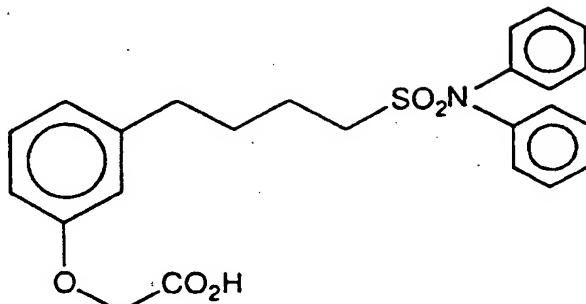
## Example 10

3-(4-Diphenylaminosulfonylbutyl)phenoxyacetic acid

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To a solution of the compound prepared in example 9 (410 mg) in ethyl acetate (5.0 ml) was added excess amount of diazomethane in ether at 0 °C. After 10 min, the mixture was evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) to give methyl ester compound (56 mg). To a solution of the methyl ester compound (56 mg) in methanol (5 ml) was added 10% palladium on activated carbon (50 mg) at room temperature. The mixture was vigorously stirred for 6h under an atmosphere of hydrogen. The catalyst was removed by filtration through Celite. Evaporation of the solvent gave (54 mg) of the residue. By the same procedure as in example 2, using the residue, the title compound (36 mg) having physical data was given.

TLC: Rf 0.21 (methylene chloride : methanol = 5 : 1).  
 IR [KBr tablet method] ( $\text{cm}^{-1}$ ):  $\nu$  2925, 2862, 2590, 1750, 1710, 1612, 1586, 1488, 1463, 1451, 1424, 1350, 1302, 1287, 1258, 1243, 1218, 1197, 1164, 1146, 1103, 1078, 1027, 1012, 978, 913, 865, 780, 759, 708, 695, 626, 594, 534.

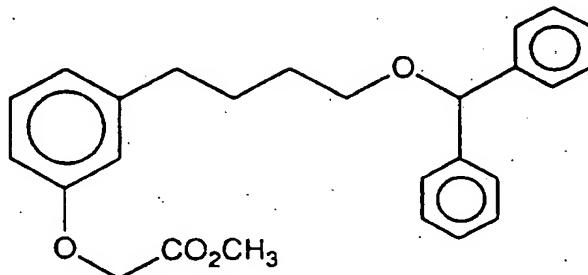
## Example 11

Methyl 3-(4-diphenylmethoxybutyl)phenoxyacetate

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To a solution of methyl 3-(4-hydroxybutyl)phenoxyacetate (372 mg) and diphenylmethyltrichloroacetimidate (771 mg) in chloroform (4 ml) and cyclohexane (8 ml) was added a catalytic amount of boron trifluoride etherate at 0 °C. After stirred for 30 min at 0 °C, the mixture was quenched by addition of a saturated aqueous solution of sodium bicarbonate, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1) to give the title compound (343 mg) having the following physical data.

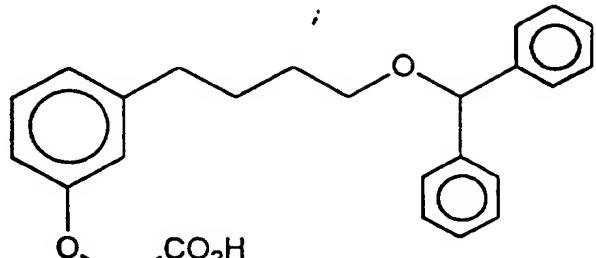
NMR:  $\delta$  7.50-7.00 (11 H, m), 6.90-6.50 (3H, m), 5.27 (1H, s), 4.58 (2H, s), 3.77 (3H, s), 3.43 (2H, t,  $J$  = 7Hz), 2.58 (2H, t,  $J$  = 7Hz), 1.68 (4H, m);

IR ( $\text{cm}^{-1}$ ):  $\nu$  3029, 2938, 2860, 1762, 1586, 1494, 1453, 1211, 1159, 1095, 1029, 743, 699.

## Example 12

3-(4-Diphenylmethoxybutyl)phenoxyacetic acid

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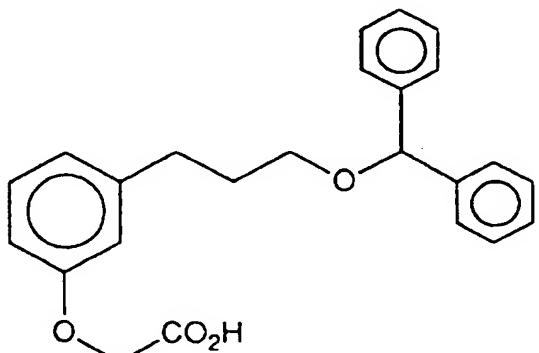
By the same procedure as in example 2, using the compound prepared in example 11 (340 mg), the title compound (277 mg) having the following physical data was given.

- 20 TLC: R<sub>f</sub> 0.18 (chloroform : methanol = 9 : 1),  
 IR (cm<sup>-1</sup>): ν 3030, 2938, 2862, 1733, 1586, 1494, 1454, 1242, 1160, 1094, 761, 744, 699.

## Example 12(a)

25 3-(3-Diphenylmethoxypropyl)phenoxyacetic acid

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By the same procedure as in example 11 → example 2, using methyl 3-(3-hydroxypropyl)-phenoxyacetate instead of methyl 3-(4-hydroxybutyl) phenoxyacetate, the title compound having the following physical data was given.

- 45 mp.: 110-112 °C;  
 TLC: R<sub>f</sub> 0.15 (ethyl acetate);  
 IR [KBr tablet method] (cm<sup>-1</sup>): ν 2861, 1748, 1710, 1594, 1494, 1431, 1398, 1307, 1237, 1174, 1105, 1083,  
 1059, 1030, 904, 859, 783, 741, 697, 651, 612.

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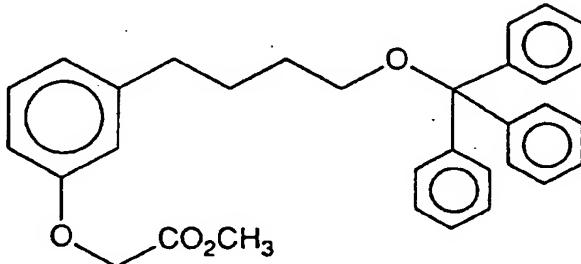
## Example 13

Methyl 3-(4-triphenylmethoxybutyl)phenoxyacetate

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To a solution of methyl 3-(4-hydroxybutyl) phenoxyacetate (174 mg) in dimethylformamide (8.0 ml) was added successively trityl chloride (223 mg) and N,N-dimethylaminopyridine (88 mg). After stirred overnight  
 20 at room temperature, the mixture was quenched by addition of water and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by flash silica gel chromatography (n-hexane: ethyl acetate = 4 : 1) to give the title compound (228 mg) having the following physical data  
 NMR: δ 7.50-7.00 (16H, m), 6.90-6.50 (3H, m), 4.58 (2H, s), 3.78 (3H, s), 3.04 (2H, t, J = 7Hz), 2.53 (2H, m),  
 25 1.66 (4H, m);  
 IR (cm<sup>-1</sup>): ν 3057, 2938, 2865, 1764, 1741, 1586, 1490, 1449, 1289, 1211, 1158, 1075, 1033, 764, 707.

## Example 14

30 3-(4-Triphenylmethoxybutyl)phenoxyacetic acid

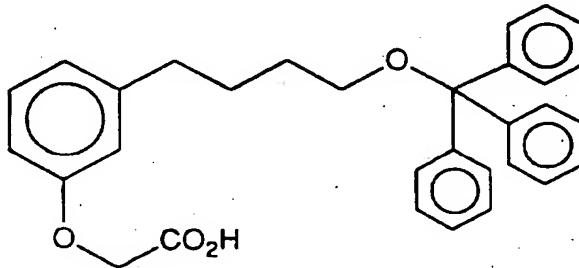
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By the same procedure as in example 2, using the compound prepared in example 13 (220 mg), the title compound (159 mg) having the following physical data was given.

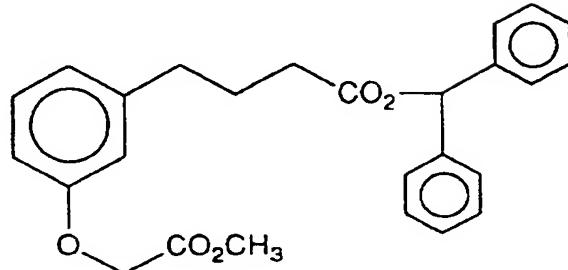
TLC: R<sub>f</sub> 0.13 (chloroform : methanol = 9 : 1);IR (cm<sup>-1</sup>): ν 3058, 2937, 2866, 1738, 1586, 1490, 1449, 1240, 1159, 1075, 900, 764, 698.

## Example 15

Methyl 3-(3-diphenylmethyloxycarbonylpropyl)phenoxyacetate

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A mixture of 3-(3-methoxycarbonylmethoxyphenyl)propionic acid (195 mg), 2-chloro-N-methylpyridinium iodide (297 mg), diphenylmethanol (185 mg), triethylamine (0.32 ml), and catalytic amount of N,N-dimethylaminopyridine in methylene chloride (6 ml) was stirred overnight at room temperature. The mixture was poured into 1N hydrochloric acid extracted with ethyl acetate. The extract was washed with water and saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1) to give the title compound (128 mg) having the following physical data.

TLC: R<sub>f</sub> 0.54 (n-hexane : ethyl acetate = 7 : 3).  
 NMR: δ 7.40-7.10 (11H, m), 6.89 (1H, s), 6.85-6.60 (3H, m), 4.60 (2H, s), 3.79 (3H, s), 2.60 (2H, t, J = 6 Hz), 2.43 (2H, t, J = 7 Hz), 1.97 (2H, m).

## Example 16

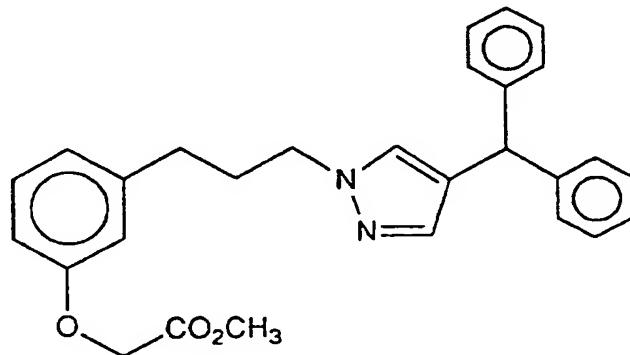
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Methyl 3-[3-(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetate

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To a suspension of sodium hydride (217 mg, 60% dispersion) in dimethylformamide (10 ml) was added dropwise a solution of 4-diphenylmethylpyrazole (1.27 g) in dimethylformamide (50 ml) at room temperature. After stirred for 30 min at room temperature, to the mixture was added dropwise a solution of the compound prepared in reference example 9 (1.56 g) in dimethylformamide. After stirred for 1h, the mixture was quenched by addition of 1N hydrochloric acid and extracted with a mixture of ethyl acetate-n-hexane (1 : 2). The extract was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 7) to give the title compound (2.01 g) having the following physical data.  
 TLC: R<sub>f</sub> 0.59 (n-hexane : ethyl acetate = 1 : 1);

EP 0 558 062 A2

NMR:  $\delta$  7.40-7.10 (12H, m), 6.93 (1H, s), 6.80-6.60 (3H, m), 5.35 (1H, s), 4.58 (2H, s), 4.03 (2H, t,  $J=7\text{Hz}$ ), 3.79 (3H, s), 2.56 (2H, t,  $J=7\text{Hz}$ ), 2.16(2H, m)

Example 17

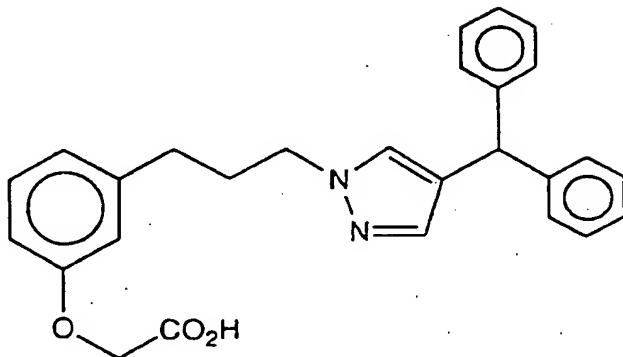
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3-[3-(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid

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By the same procedure as in example 2, using the compound prepared in example 16 (1.5 g), the title  
25 compound (1.1 g) having the following physical data was given.

TLC: Rf 0.21 (chloroform : methanol = 4 : 1);

IR [KBr tablet method] ( $\text{cm}^{-1}$ ):  $\nu$  3027, 2930, 1736, 1586, 1493, 1451, 1219, 1159, 1079, 1014, 874, 753,  
701, 507.

30 Example 17(a)-17(dd)

By the same procedure as in reference example 9 → example 16 → example 17, using corresponding compounds, compounds having the following physical data shown in the table 5 were given.

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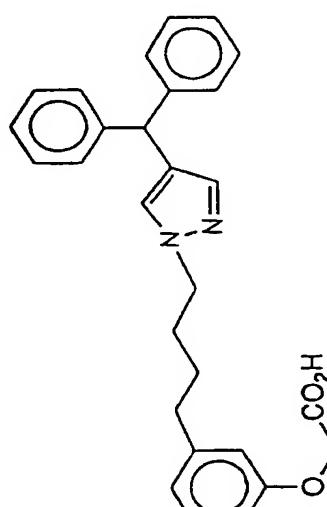
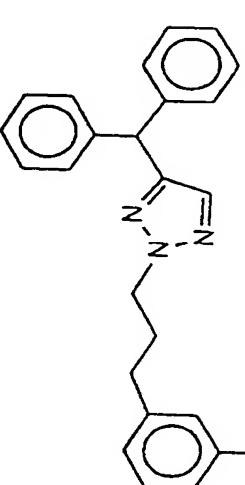
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Table 5

EX. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
1.7 (a)		Rf 0.26 (chloroform : methanol = 4:1)	$\nu$ 3021, 2936, 2861, 2517, 1736, 1556, 1494, 1451, 1374, 1219, 1158, 1079, 1015, 873, 753, 700, 635, 596, 475
1.7 (b)		Rf 0.19 (chloroform : methanol = 4:1)	$\nu$ 3029, 2932, 1737, 1581, 1494, 1452, 1373, 1212, 1160, 1080, 1022, 848, 780, 753, 700

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Table 5 (continued)

EX. No.	Structure of the example compound	TLC	IR ( $\text{cm}^{-1}$ )
17 (c)		Rf 0.15 (chloroform : methanol = 4:1)	3028, 2929, 1736, 1586, 1494, 1452, 1216, 1160, 1079, 878, 754, 699, 637.
17 (d)		Rf 0.14 (chloroform : methanol = 4:1)	3029, 2929, 2508, 1736, 1586, 1493, 1454, 1222, 1160, 1114, 1081, 1032, 848, 751 701, 639 = 4:1)

Table 5 (continued)

Ex. No.	Structure of the example compound	TLC (R <sub>f</sub> )	N M R (δ)
17(e)		0.60 ( methanol: methylenec chloride = 1 : 4 )	7.30-7.00 (12H, m), 6.96 (1H, s), 6.90-6.80 (2H, m), 6.76 (1H, d), 5.30 (1H, s), 4.60 (2H, s), 4.10 (2H, t), 2.67 (2H, t), 1.83 (2H, m), 1.60 (2H, m).
17(f)		0.63 ( methanol: methylenec chloride = 1 : 4 )	7.50 (1H, brs), 7.35-7.00 (13H, m), 6.93 (1H, s), 6.90 (1H, t), 6.75 (1H, d), 5.30 (1H, s), 4.60 (2H, s), 4.05 (2H, t), 2.67 (2H, t), 1.85 (2H, m), 1.63 (2H, m), 1.30 (2H, m).

Table 5 (continued)

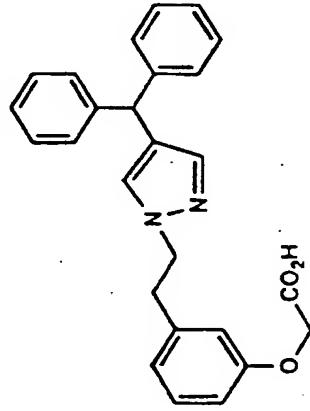
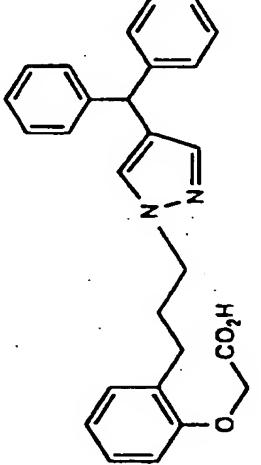
EX. No.	Structure of the example compound	TLC (Rf)	N M R ( $\delta$ )
17(g)		0.19 ( methanol: methylene chloride = 1 : 5 )	7.4-7.0 (12H, m), 6.82 (2H, m), 6.72 (1H, s), 6.67 (1H, t), 6.04-6.08 (1H, brs), 5.28 (1H, s), 4.58 (2H, s), 4.29 (2H, t), 3.05 (2H, t)
17(h)		0.33 ( methanol: methylene chloride = 1 : 5 )	8.0-7.2 (1H, brs), 7.4-7.0 (13H, m), 7.02 (1H, s), 6.92 (1H, t), 6.76 (1H, d), 5.32 (1H, s), 4.58 (2H, s), 4.08 (2H, t), 2.66 (2H, t), 2.17 (2H, t)

Table 5 (continued)

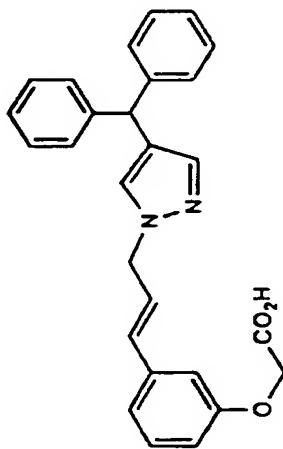
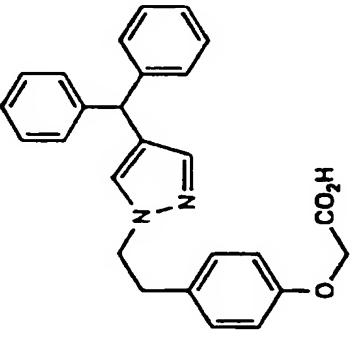
EX. No.	Structure of the example compound	TLC (Rf)	N M R ( $\delta$ )
17(i)		0.26 (chloroform : methanol = 4 : 1)	7.95 (1H, brs), 7.36-7.13 (12H, m), 7.05 (1H, s), 6.96 (1H, d), 6.92 (1H, m), 6.78 (1H, dd), 6.48 (1H, d), 6.29 (1H, dt), 5.33 (1H, s), 4.82 (2H, d), 4.56 (2H, s).
17(j)		0.24 (methanol : methylene chloride = 1 : 5)	(CDCl <sub>3</sub> -CD <sub>3</sub> OD) 7.4-7.0 (11H, m), 6.94 (2H, d), 6.80 (2H, d), 6.72 (1H, s), 5.26 (1H, s), 4.56 (2H, s), 4.20 (2H, t), 3.03 (2H, t)

Table 5 (continued)

Ex. No.	Structure of the example compound	TLC (R <sup>f</sup> )	N M R (δ)
17(k)		0.26 ( methanol: methylene chloride = 1 : 5 )	7.5-7.1 (11H, m), 7.01 (2H, d), 6.95 (1H, s), 6.82 (2H, d), 5.34 (1H, s), 4.58 (2H, s), 4.07 (2H, t), 2.49 (2H, t), 2.08 (2H, tt)
17(l)		0.28 ( methanol: methylene chloride = 1 : 5 )	7.5-7.1 (11H, m), 7.02 (2H, d), 6.96 (1H, s), 6.82 (2H, d), 6.6-5.6 (1H, brs), 5.33 (1H, s), 4.59 (2H, s), 4.07 (2H, t), 2.52 (2H, t), 1.82 (2H, m), 1.51 (2H, m).

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Table 5 (continued)

EX. No.	Structure of the example compound	TLC (RI)	N M R (δ)
17(m)		0.17  (methanol: methylene chloride = 1 : 5)	7.4-7.3 (12H, m), 7.05 (1H, s), 6.9-6.7 (3H, m), 5.32 (1H, s), 5.20 (2H, s), 4.58 (2H, s).
17(n)		0.31  (chloroform : methanol = 4 : 1)	8.70-8.00 (3H, m), 7.75-7.50 (1H, m), 7.35-6.97 (9H, m), 6.94-6.70 (3H, m), 5.43 (1H, brs), 5.30 (2H, brs), 4.08 (2H, m), 2.72 (2H, m), 2.06-1.50 (4H, m).

Table 5 (continued)

Ex. No.	Structure of the example compound	TLC (RI)	N M R ( $\delta$ )
17(o)		0.16 ( methanol: methylene chloride = 1:5 )	8.47 (2H, m), 7.61 (1H, d), 7.40-7.13 (8H, m), 7.09 (1H, s), 7.00-6.80 (3H, m), 6.43 (1H, d), 6.27 (1H, d), 5.42 (1H, s), 4.87 (2H, d), 4.62 (2H, s).
17(p)		0.29 (chloroform : methanol = 4:1)	7.36-7.13 (11H, m), 6.95 (1H, s), 6.94-6.70 (4H, m), 5.33 (1H, s), 4.75 (2H, s), 4.03 (2H, t), 3.84 (3H, s), 2.50 (2H, t), 2.20-2.02 (2H, m).

Table 5 (continued)

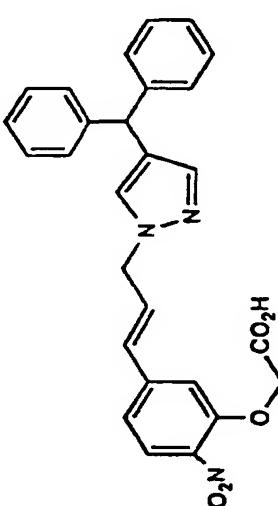
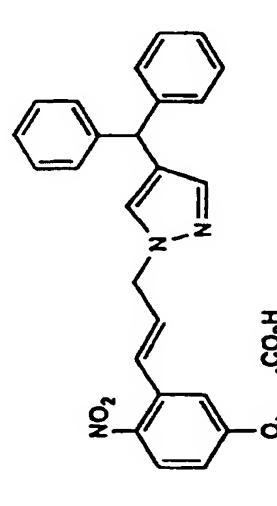
EX. No.	Structure of the example compound	TLC (R <sub>f</sub> )	N M R (δ)
17(q)	 17(q)	0.28 ( methanol: methylene chloride = 1 : 5 )	7.83 (1H, d), 7.4-7.1 (11H, m), 7.07 (1H, s), 7.00 (1H, dd), 6.97 (1H, d), 6.6-5.8 (1H, brs), 6.43 (2H, m), 5.35 (1H, s), 4.87 (2H, m), 4.75 (2H, s).
17(r)	 17(r)	0.22 ( methanol: methylene chloride = 1 : 5 )	8.02 (1H, d), 7.40 (1H, s), 7.4-7.1 (11H, m), 7.07 (1H, d), 7.03 (1H, d), 6.88 (1H, dd), 6.32 (1H, d), 6.2-5.2 (1H, brs), 5.36 (1H, s), 4.90 (2H, d), 4.68 (2H, s).

Table 5 (continued)

EX. No.	Structure of the example compound	TLC (R <sub>f</sub> )	N M R (δ)
17(s)		0.32 (chloroform : methanol = 4 : 1)	7.38-6.98 (14H, m), 6.17 (1H, d), 6.65 (1H, t), 5.44 (1H, brs), 5.36 (1H, s), 4.88 (2H, d), 4.57 (2H, s), 2.20 (3H, s).
17(l)		0.38 (chloroform : methanol = 4 : 1)	7.38-7.00 (13H, m), 7.00-6.60 (1H, brs), 6.86 (1H, d), 6.74 (1H, s), 6.47 (1H, d), 6.24 (1H, d), 5.32 (1H, s), 4.79 (2H, d), 4.62 (2H, s), 2.24 (3H, s).

Table 5 (continued)

EX. No.	Structure of the example compound	TLC (R <sub>f</sub> )	N M R (δ)
17(u)		0.32 (chloroform : methanol = 4 : 1)	7.38-7.00 (12H, m), 7.00-6.20 (1H, brs), 6.78 (1H, s), 6.70 (1H, s), 6.63 (1H, s), 6.43 (1H, d), 6.26 (1H, dt), 5.33 (1H, s), 4.81 (2H, d), 4.56 (2H, s), 2.26 (3H, s).
17(v)		0.31 (chloroform : methanol = 4 : 1)	7.40-6.90 (14H, m), 6.74 (1H, dd), 6.63 (1H, d), 6.40 (1H, brs), 6.20 (1H, dt), 5.35 (1H, s), 4.85 (2H, d), 4.57 (2H, s), 2.20 (3H, s).

Table 5 (continued)

EX. No.	Structure of the example compound	TLC (R <sub>f</sub> )	N M R (δ)
17(w)		0.40 ( methanol: methylene chloride = 1 : 4 )	8.63 and 8.47 (1H, s), 8.56 and 8.53 (1H, d), 7.78-7.73 and 7.62-7.37 (1H, m), 7.45-7.22 (6H, m), 7.16-7.09 (1H, m), 6.79-6.65 (3H, m), 4.43 (2H, s), 4.38-4.33 (2H, m), 2.96-2.88 (2H, m)
17(x)		0.49 ( methanol: methylene chloride = 1 : 4 )	8.71 and 8.62 (1H, s), 8.61 and 8.55 (1H, d), 7.80-7.76 and 7.70-7.67 (1H, m), 7.50-7.25 (6H, m), 7.13-7.06 (1H, m), 6.75-6.65 (3H, m), 4.45 (2H, s), 4.20-4.10 (2H, m), 2.60-2.50 (2H, m), 2.01-1.92 (2H, m)

Table 5 (continued)

Ex. No.	Structure of the example compound	TLC (R <sub>f</sub> )	N M R ( $\delta$ )
17(y)		0.46 ( methanol: methylenec chloride = 1 : 4 )	8.81 and 8.67 (1H, s), 8.57 and 8.52 (1H, d), 7.73-7.65 (1H, m), 7.50-7.20 (6H, m), 7.10-7.05 (2H, m), 6.85 (1H, t), 6.73 (1H, d), 4.51 and 4.48 (2H, s), 4.25-4.18 (2H, m), 2.75-2.65 (2H, m), 2.10-1.98 (2H, m)
17(z)		0.46 ( methanol: methylenec chloride = 1 : 4 )	8.71 and 8.62 (1H, s), 8.55 and 8.52 (1H, d), 7.78-7.74 and 7.70-7.66 (1H, m), 7.47-7.15 (6H, m), 7.13-7.08 (2H, m), 6.88 (1H, t), 6.74 (1H, d), 4.54 (2H, s), 4.25-4.18 (2H, m), 2.73-2.65 (2H, m), 1.80-1.60 (4H, m).

Table 5 (continued)

EX. No.	Structure of the example compound	TLC (Rf)	N M R ( $\delta$ )
17(aa)		0.43 ( methanol: methylenec chloride = 1 : 4 )	8.72 and 8.64 (1H, s), 8.59-8.50 (1H, m), 7.78-7.73 and 7.68-7.65 (1H, m), 7.46-7.15 (6H, m), 7.14-7.07 (2H, m), 6.90-6.85 (1H, m), 6.78-6.73 (1H, m), 4.52 (2H, s), 4.18 (2H, t), 2.67 (2H, t), 1.80-1.69 (2H, m), 1.69-1.56 (2H, m), 1.44-1.34 (2H, m)
17(bb)		0.22 ( methanol: methylenec chloride = 1 : 5 )	8.80 (0.4H, d), 8.70 (0.6H, d), 8.67 (0.6H, dd), 8.62 (0.4H, dd), 7.87-7.72 (1H, m), 7.60-6.90 (9H, m), 6.90-6.78 (1H, m), 6.63 (0.4H, d), 6.55 (0.6H, d), 6.37 (0.6H, dd), 6.30 (0.4H, dt), 4.92-4.77 (2H, m), 4.67 (0.8H, s), 4.65 (1.2H, s),

Table 5 (continued)

EX. No.	Structure of the example compound	TLC (RI)	N M R ( $\delta$ )
17(cc)		0.19 ( methanol: methylene chloride = 1 : 5 )	7.4-7.0 (12H, m), 6.8-6.0 (5H, m), 5.32 (1H, s), 4.58 (2H, s), 4.44 (2H, t), 4.24 (2H, t)
17(dd)		0.43 ( methanol: methylene chloride = 1 : 4 )	8.67 and 8.57 (1H, s), 8.56 and 8.53 (1H, d), 7.77-7.73 and 7.70-7.65 (1H, m), 7.45-7.25 (6H, m), 7.13-7.06 (1H, m), 6.55-6.45 (3H, m), 4.55-4.40 (4H, m), 4.25-4.15 (2H, m)

The example compounds shown in the table 5 are named as follows:

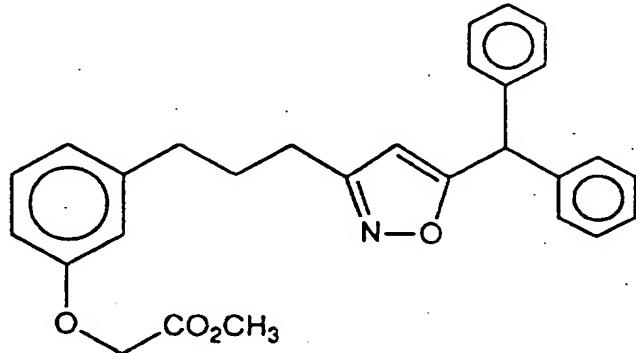
- 17(a) 3-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,  
 17(b) 3-[3-(4-Diphenylmethyl-1,2,3-triazol-2-yl)propyl]phenoxyacetic acid  
 17(c) 3-[3-(4-Diphenylmethyl-1,2,3-triazol-1-yl)propyl]phenoxyacetic acid  
 17(d) 3-[3-(4-Diphenylmethyl-1,2,3-triazol-3-yl)propyl]phenoxyacetic acid,

EP 0 558 062 A2

- 17(e) 2-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,
- 17(f) 2-[5-(4-Diphenylmethylpyrazol-1-yl)pentyl]phenoxyacetic acid,
- 17(g) 3-[2-(4-Diphenylmethylpyrazol-1-yl)ethyl]phenoxyacetic acid,
- 17(h) 2-[3-(4-Diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid,
- 5 17(i) 3-[3-(4-Diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid.
- 17(j) 4-[2-(4-Diphenylmethylpyrazol-1-yl)ethyl]phenoxyacetic acid,
- 17(k) 4-[3-(4-Diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid..
- 17(l) 4-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,
- 17(m) 3-[4-(4-Diphenylmethylpyrazol-1-yl)methyl]phenoxyacetic acid.
- 10 17(n) 2-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,
- 17(o) 3-[3-[4-(1-Phenyl-1-(3-pyridyl)methyl)pyrazol-1-yl]-1-propenyl]phenoxy acetic acid,
- 17(p) 2-Methoxy-5-[3(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid,
- 17(q) 2-Nitro-5-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,
- 17(r) 4-Nitro-3-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,
- 15 17(s) 2-Methyl-3-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,
- 17(t) 2-Methyl-5-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,
- 17(u) 3-Methyl-5-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,
- 17(v) 4-Methyl-3-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,
- 17(w) 3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]ethyl]phenoxyacetic acid,
- 20 17(x) 3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]propyl]phenoxyacetic acid.
- 17(y) 2-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]propyl]phenoxyacetic acid,
- 17(z) 2-[4-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]butyl]phenoxyacetic acid,
- 17(aa) 2-[5-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]pentyl]phenoxy acetic acid,
- 17(bb) 3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]-1-propenyl]phenoxy acetic acid,
- 25 17(cc) 3-[2-(4-Diphenylmethylpyrazol-1-yl)ethyloxy]phenoxyacetic acid,
- 17(dd) 3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminoxy]ethyloxy]phenoxy acetic acid

Example 18

- 30 Methyl 3-[3-(5-diphenylmethylisoxazol-3-yl)propyl]phenoxyacetate



To a suspension of the compound prepared in reference example 16 (300 mg), potassium bicarbonate (138 mg) in dimethylformamide (4.0 ml) was added dropwise methyl bromoacetate (0.095 ml) with stirring at room temperature. The mixture was stirred for 5h at 50 °C. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (benzene : ethyl acetate = 19 : 1) to give the title compound (350 mg) having the following physical data

55 TLC: R<sub>f</sub> 0.22 (ethyl acetate : n-hexane = 1:3);  
 NMR: δ 7.37-7.02 (11H, m), 6.85-6.67 (3H, m), 5.72 (1H, s), 5.51 (1H, s), 4.62 (2H, s), 3.79 (3H, s), 2.72-2.57 (4H, m), 2.05-1.86 (2H, m).

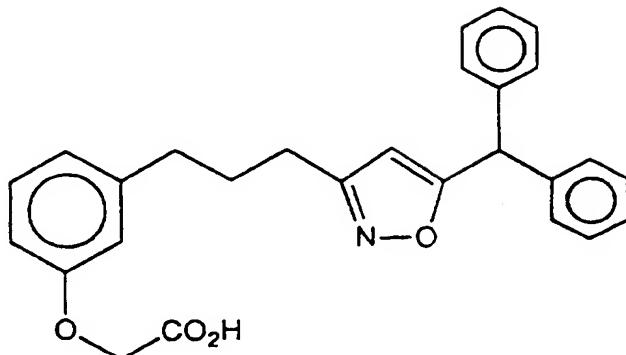
## Example 19

3-[3-(5-diphenylmethylisoxazol-3-yl)propyl]phenoxyacetic acid

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To a solution of the compound prepared in example 18 (295 mg) in tetrahydrofuran (2.0 ml) and methanol (1.0 ml) was added dropwise 1N aqueous solution of sodium hydroxide (1.0 ml) with stirring at room temperature. After stirred for 30 min at room temperature. After neutralized by addition of 1N hydrochloric acid, the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol = 49 : 1 → 9 : 1) to give the title compound (208 mg) having the following physical data.

TLC: R<sub>f</sub> 0.25 (chloroform : methanol = 4 : 1);

IR [KBr tablet method] (cm<sup>-1</sup>): ν 3401, 3028, 2924, 1796, 1494, 1452, 1425, 1340, 1248, 1160, 1078, 900, 791, 752, 699

## Example 19(a)-19(b)

By the same procedure as in reference example 14 → reference example 16 → example 18 → example 35 19, using the compound prepared in reference example 23 and by the same procedure as in reference example 16 → example 18 → example 19, using the compound prepared in reference example 25, compounds having the following physical data shown in the table 6 were given.

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Table 6

EX. No.	Structure of the example compound	TLC (Rf)	N M R ( $\delta$ )
19(a)		0.14 (chloroform :methanol = 9 : 1)	7.4-6.5 (1H, brs), 7.38-7.14 (11H, m), 6.82 (1H, d), 6.77-6.72 (2H, m), 5.81 (1H, s), 5.55 (1H, s), 4.65 (2H, s), 2.71 (2H, t), 2.65 (2H, t), 2.09-1.92 (2H, m).
19(b)		0.19 (chloroform :methanol = 17 : 3)	7.35-7.12 (11H, m), 6.84-6.69 (4H, m), 5.97 (1H, brs), 5.66 (1H, s), 4.64 (2H, s), 2.85 (2H, t), 2.64 (2H, t), 2.08-1.90 (2H, m).

The example compounds shown in the table 6 are named as follows

19(a) 3-[3-(3-Diphenylmethylisoxazol-5-yl)propyl]phenoxyacetic acid

19(b) 3-[3-(3-Diphenylmethylisothiazol-5-yl)propyl]phenoxyacetic acid

## Example 20

Methyl 3-[3-(3-diphenylmethyl-1,2,4-oxadiazol-5-yl)propyl]phenoxy acetate

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A solution of the compound prepared in reference example 17 (193 mg) in toluene (8 ml) was refluxed overnight. The mixture was evaporated. The residue was purified by flash silica gel chromatography (n-hexane : ethyl acetate = 4 : 1) to give the title compound (108 mg) having the following physical data.

NMR:  $\delta$  7.40-7.10 (11H, m), 6.90 (1H, d,  $J$  = 7Hz), 6.75 (1H, s), 6.72 (1H, d,  $J$  = 7Hz), 5.58 (1H, s), 4.60 (2H, s), 3.79 (3H, s), 2.87 (2H, t,  $J$  = 7Hz), 2.67 (2H, t,  $J$  = 7Hz), 2.11 (2H, m);  
 MS(m/z): 442 ( $M^+$ ), 250, 167.

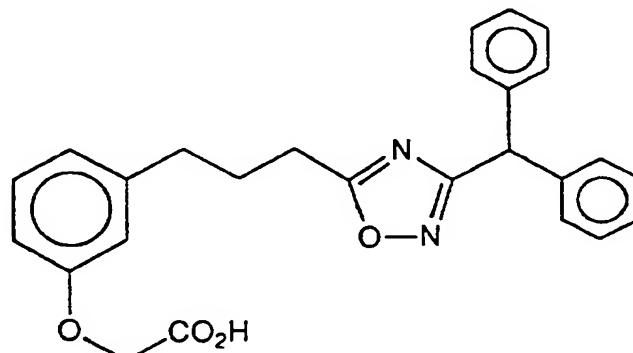
## Example 21

30 3-[3-(3-diphenylmethyl-1,2,4-oxadiazol-5-yl)propyl]phenoxyacetic acid

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By the same procedure as in example 2, using the compound prepared in example 20 (108 mg), the title compound (102 mg) having the following physical data was given

TLC: Rf 0.16 (chloroform : methanol = 9 : 1),  
 NMR:  $\delta$  7.40-7.10 (11H, m), 6.90-6.70 (3H, m), 5.59 (1H, s), 4.62 (2H, s), 2.87 (2H, t,  $J$  = 7Hz), 2.68 (2H, t,  $J$  = 7Hz), 2.12 (2H, m).

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## Example 22

Methyl 3-[3-(5-diphenylmethyl-1,2,4-oxadiazol-3-yl)propyl]phenoxy acetate

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A solution of the compound prepared in reference example 20 (61 mg) in toluene (8.0 ml) was refluxed overnight. The mixture was evaporated. The residue was purified by flash silica gel chromatography (n-hexane : ethyl acetate = 4 : 1) to give the title compound (31 mg) having the following physical data.

NMR:  $\delta$  7.40-7.10 (11H, m), 6.82 (1H, d,  $J$  = 7Hz), 6.78 (1H, s), 6.74 (1H, d,  $J$  = 7Hz), 5.70 (1H, s), 4.60 (2H, s), 3.80 (3H, s), 2.76 (2H, t,  $J$  = 7Hz), 2.67 (2H, t,  $J$  = 7Hz), 2.08 (2H, m),

MS (m/z): 442 ( $M^+$ ), 251, 167.

## Example 23

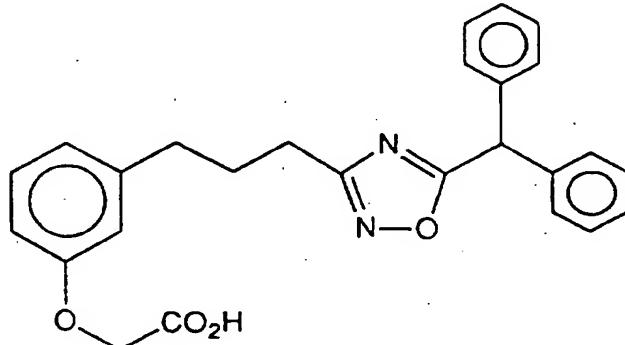
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3-[3-(5-diphenylmethyl-1,2,4-oxadiazol-3-yl)propyl]phenoxyacetic acid



By the same procedure as in example 2, using the compound prepared in example 22 (31 mg), the title compound (30 mg) having the following physical data was given

TLC: Rf 0.18 (chloroform : methanol = 9 : 1);

NMR:  $\delta$  7.40-7.10 (11H, m), 6.84 (1H, d,  $J$  = 7Hz), 6.77 (1H, s), 6.74 (1H, d,  $J$  = 7Hz), 5.72 (1H, s), 4.63 (2H, s), 2.74 (2H, t,  $J$  = 7Hz), 2.67 (2H, t,  $J$  = 7Hz), 2.08 (2H, m).

## Formulation example 1

55

The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 5 mg of active ingredient

• 3-(4-Diphenylmethoxyiminobutyl)phenoxy acetic acid	500mg
• Carboxymethylcellulose calcium	200 mg
• Magnesium stearate	100 mg
• Microcrystalline cellulose	9.2 g

5

## Formulation example 2

10 The following components were admixed in conventional manner. The solution was sterilized in conventional manner, placed 5 ml portion into 10 ml ampoules and freeze-dried to obtain 100 ampoules each containing 2 mg of the active ingredient.

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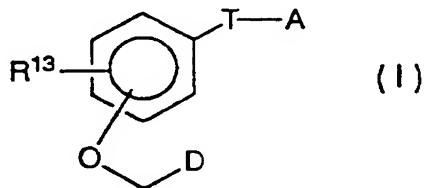
• 3-(4-Diphenylmethoxyiminobutyl)phenoxy acetic acid	200 mg
• Citric acid, anhydrous	20 mg
• Distilled water	500 ml

20 "While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof "

## Claims

25 1. A Phenoxyacetic acid derivative of the formula (I)

30



35

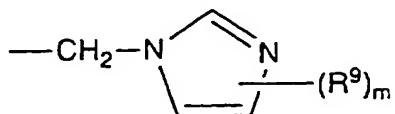
wherein

A is

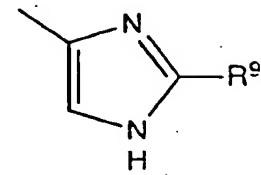
- i)  $-Cr^1=N-OR^2$ ,
- ii)  $-CHR^1-NH-OR^2$ ,
- iii)  $-COE$ ,
- iv)  $-SO_2E$ ,
- v)  $-CH_2-NR^3-Y$ ,
- vi)  $-Z-NR^3-CONR^4R^5$ ,
- vii)  $-CH_2-OR^6$ ,
- viii)  $-CO_2R^6$ ,
- ix)  $-CH_2-O-N=CR^7R^8$ ,
- x)  $-CH_2-O-NHCHR^7R^8$ ,
- xi)

50

55

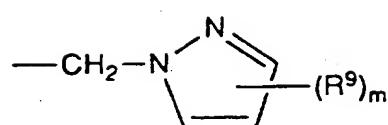


xii)



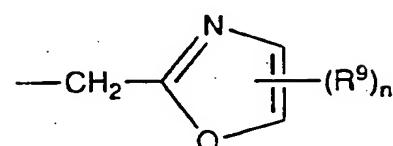
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xiii)



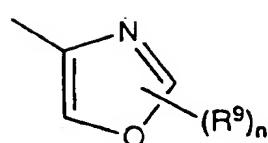
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xiv)



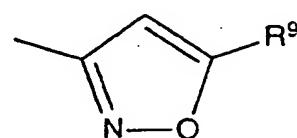
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xv)



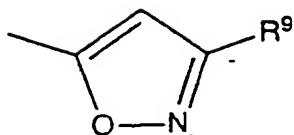
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xvi)



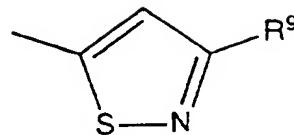
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xvii)

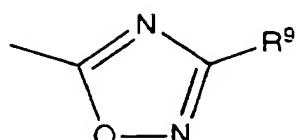


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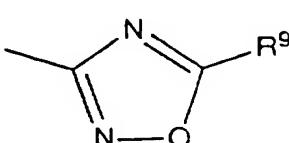
xviii)



xix)

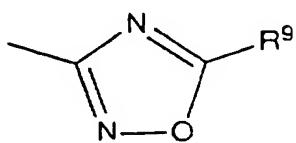


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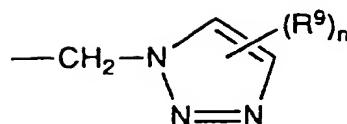


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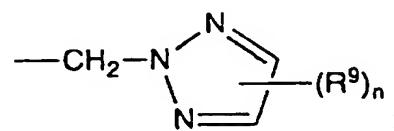
xx)



xxi)



35

or  
xxii)

45

T      is

- i) single bond,
- ii) C1-6 alkylene,
- iii) C2-6 alkenylene or
- iv) -O-(CH<sub>2</sub>)<sub>5</sub>-.

50

D      is

- i) -CO<sub>2</sub>R<sup>10</sup> or
- ii) -CONR<sup>11</sup>R<sup>12</sup>.

55

E      is

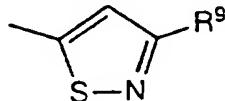
- i) -NR<sup>4</sup>R<sup>5</sup>,
- ii) -NR<sup>3</sup>OR<sup>6</sup>,
- iii) -NR<sup>3</sup>-NR<sup>4</sup>R<sup>5</sup> or

		iv) -NR <sup>3</sup> -N=CR <sup>4</sup> R <sup>5</sup> ;
Y	IS	i) -COR <sup>6</sup> , ii) -CO-L-NR <sup>4</sup> R <sup>5</sup> , iii) -CS-NHR <sup>4</sup> or iv) -SO <sub>2</sub> R <sup>6</sup> ,
5		
Z	IS	i) -CN=N- or ii) -CH <sub>2</sub> -NR <sup>3</sup> -;
10	L	is single bond or C1-4 alkylene
R <sup>1</sup>		is hydrogen, C1-6 alkyl or phenyl;
R <sup>2</sup>	IS	i) C1-8 alkyl substituted by one or two of phenyl, 4-7 membered monocyclic hetero ring containing one nitrogen or C4-7 cycloalkyl, ii) C10-15 hydrocarbon condensed tricyclic ring or iii) C1-15 alkyl;
15	R <sup>3</sup>	is hydrogen, C1-6 alkyl or phenyl,
R <sup>4</sup> and R <sup>5</sup>		each, independently, is i) hydrogen, ii) phenyl, iii) 4-7 membered monocyclic hetero ring containing one nitrogen or iv) C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen.
20	R <sup>6</sup>	IS i) phenyl, ii) 4-7 membered monocyclic hetero ring containing one nitrogen or iii) C1-4 alkyl substituted by one to three of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen.
25	R <sup>7</sup>	IS i) hydrogen, ii) C1-8 alkyl, iii) phenyl or C4-7 cycloalkyl, iv) 4-7 membered monocyclic hetero ring containing one nitrogen or v) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
30	R <sup>8</sup>	IS i) C1-8 alkyl, ii) phenyl or C4-7 cycloalkyl iii) 4-7 membered monocyclic hetero ring containing one nitrogen or iv) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
35	R <sup>9</sup>	IS i) hydrogen, ii) phenyl, iii) C1-4 alkyl or iv) C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
40	R <sup>10</sup>	is hydrogen or C1-12 alkyl.
R <sup>11</sup> and R <sup>12</sup>		each, independently, is hydrogen or C1-4 alkyl or taken together with nitrogen bond to R <sup>11</sup> and R <sup>12</sup> is the residue of an amino acid;
R <sup>13</sup>		is hydrogen, C1-4 alkyl, C1-4 alkoxy or nitro,
m		is 1-3,
n		is 1-2,
s		is 2-4;
55		and the rings of R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> , R <sup>4</sup> , R <sup>5</sup> , R <sup>6</sup> , R <sup>7</sup> , R <sup>8</sup> and R <sup>9</sup> may be also substituted by one to three of C1-C4 alkyl, C1-C4 alkoxy, halogen, nitro or trihalomethyl. with the proviso that.

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- 1) when A is  $-\text{SO}_2\text{E}$  wherein E is the same meaning hereinbefore defined, T is not single bond and C1 alkylene (methylene),  
2) when A is

6



10

wherein in R9 is the same meaning hereinbefore defined, T is not C2-C6 alkenylene, and non-toxic salts thereof and non-toxic acid addition salts thereof.

2. A compound according to claim 1, wherein D is carboxy.  
15 3. A compound according to claim 1, wherein D is C1-12 alkoxy carbonyl.  
4. A compound according to claim 1, wherein D is  $\text{CONR}^{11}\text{R}^{12}$  in which R<sup>11</sup> and R<sup>12</sup> are the same meaning as defined in claim 1.

20

5. A compound according to claim 1, wherein

A is

- i)  $-\text{CR}^1=\text{N}-\text{OR}^2$ ,  
ii)  $-\text{CHR}^1-\text{NH}-\text{OR}^2$ ,  
25 ix)  $-\text{CH}_2-\text{O}-\text{N}=\text{CR}^7\text{R}^8$  or  
x)  $-\text{CH}_2-\text{O}-\text{NHCHR}^7\text{R}^8$

in which all the symbols are the same meaning as defined in claim 1.

30

6. A compound according to claim 1, wherein

A is

- iii) -COE,  
iv)  $-\text{SO}_2\text{E}$   
v)  $-\text{CH}_2\text{NR}^3\text{Y}$  or  
vi)  $-\text{Z}-\text{NR}^3-\text{CONR}^4\text{R}^5$

35 in which all the symbols are the same meaning as defined in claim 1

30

7. A compound according to claim 1, wherein

A is

- vii)  $-\text{CH}_2\text{OR}^6$

40 in which R<sup>6</sup> is the same meaning as defined in claim 1.

40

8. A compound according to claim 1, wherein

A is

- viii)  $-\text{CO}_2\text{R}^6$

45 in which R<sup>6</sup> is the same meaning as defined in claim 1.

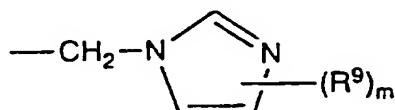
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9. A compound according to claim 1, wherein

A is

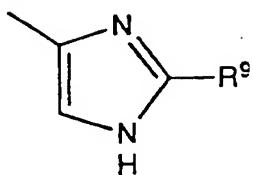
- xi)

55



xii)

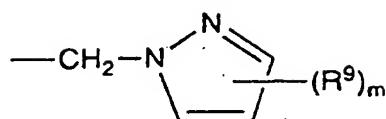
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10

Or  
xiii)

15



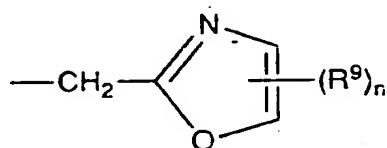
in which all the symbols are the same meaning as defined in claim 1.

20

10. A compound according to claim 1, wherein

A is  
xiv)

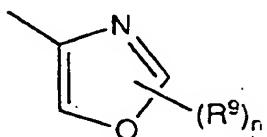
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xv)

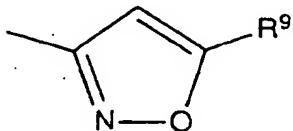
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xvi)

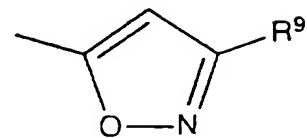
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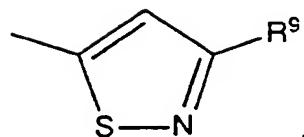
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xvii)

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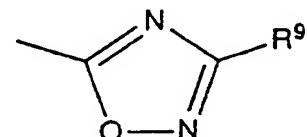


xviii)



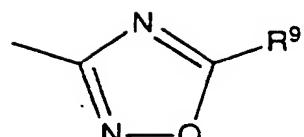
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xix)



25

or  
xx)



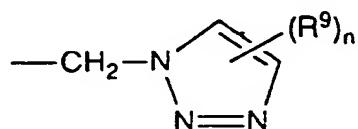
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in which all the symbols are the same meaning as defined in claim 1.

40 11. A compound according to claim 1, wherein

A is

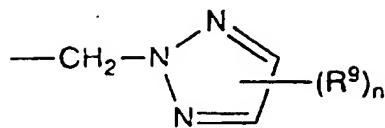
xxi)



50

or  
xxii)

55



in which all the symbols are the same meaning as defined in claim 1

- 10 12. A compound according to claim 5, which is  
 3-(4-Diphenylmethoxyiminobutyl)phenoxyacetic acid,  
 4-(3-Diphenylmethoxyiminoethyl)phenoxyacetic acid,  
 4-(4-Diphenylmethoxyiminoethyl)phenoxyacetic acid,  
 3-(3-Diphenylmethoxyiminoethyl)phenoxyacetic acid,  
 5 3-(4-Diphenylmethoxyiminoheptyl)phenoxyacetic acid,  
 3-(4-Diphenylmethoxyaminoheptyl)phenoxyacetic acid,  
 3-[2-[2-Phenyl-2-(3-pyridyl)ethyl]oxyiminoethyl]phenoxyacetic acid,  
 3-[2-[2-Cyclohexyl-2-phenylethyl]oxyiminoethyl]phenoxyacetic acid,  
 3-[2-[2-(Fluorene-9-yl)ethyl]oxyiminoethyl]phenoxyacetic acid,  
 20 3-[2-(2-Phenyldecyl)oxyiminoethyl]phenoxyacetic acid,  
 3-[2-Di(3-pyridyl)methoxyiminoethyl]phenoxyacetic acid,  
 3-[4-Methyl-4-(1-phenyl-1-(3-pyridyl)methoxyimino)butyl]phenoxyacetic acid,  
 3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]ethyl]phenoxyacetic acid,  
 25 3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,  
 2-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,  
 2-[4-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]butyl]phenoxyacetic acid,  
 2-[5-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]pentyl]phenoxyacetic acid  
 3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]-1-propenyl]phenoxyacetic acid,  
 30 3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]ethoxy]phenoxyacetic acid,  
 3-[3-[Di(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,  
 3-[3-[1-Cyclohexyl-1-phenylmethylideneaminooxy]propyl]phenoxyacetic acid  
 2-Methyl-3-[3-[1-phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,  
 3-[3-[1-Phenyl-1-(3-pyridyl)methylaminooxy]propyl]phenoxyacetic acid  
 or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.
- 35 13. A compound according to claim 6, which is  
 3-(3,3-Diphenylpropylaminocarbonylmethyl)phenoxyacetic acid,  
 3-(N-Benzyl-N-phenylaminocarbonylmethyl)phenoxyacetic acid,  
 3-(N,N-Dibenzylaminocarbonylmethyl)phenoxyacetic acid,  
 40 3-(N-Benzylaminocarbonylmethyl)phenoxyacetic acid,  
 3-(Diphenylmethylaminocarbonylmethyl)phenoxyacetic acid,  
 3-[(N,N-Diphenylamino)aminocarbonylmethyl]phenoxyacetic acid,  
 3-(1,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,  
 45 3-(2,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,  
 3-(Diphenylmethoxyaminocarbonylmethyl)phenoxyacetic acid,  
 3-[(1,1-Diphenylmethyldieneamino)aminocarbonylmethyl]phenoxyacetic acid,  
 3-[3-(3,3-Diphenylpropylaminocarbonyl)propyl]phenoxyacetic acid,  
 50 3-[3-(N-Benzyl-N-phenylaminocarbonyl)propyl]phenoxyacetic acid,  
 3-[3-(N,N-Dibenzylaminocarbonyl)propyl]phenoxyacetic acid,  
 3-(3-Benzylaminocarbonylpropyl)phenoxyacetic acid,  
 3-(3-Diphenylmethylaminocarbonylpropyl)phenoxyacetic acid,  
 55 3-[3-(N,N-Diphenylamino)aminocarbonyl]propyl]phenoxyacetic acid,  
 3-[3-(1,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,  
 3-[3-(2,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,  
 3-(3-Diphenylmethoxyaminocarbonylpropyl)phenoxyacetic acid,  
 3-[3-(1,1-Diphenylmethyldieneamino)aminocarbonyl]propyl]phenoxyacetic acid,  
 3-[2-(3,3-Diphenylpropylaminocarbonyl)ethyl]phenoxyacetic acid,  
 3-[2-(N-Benzyl-N-phenylaminocarbonyl)ethyl]phenoxyacetic acid,

3-[2-(N,N-Dibenzylaminocarbonyl)ethyl]phenoxyacetic acid,  
 3-(2-Benzylaminocarbonylethyl)phenoxyacetic acid,  
 3-(2-Diphenylmethylaminocarbonylethyl)phenoxyacetic acid,  
 5 3-[2-[(N,N-Diphenylamino)aminocarbonyl]ethyl]phenoxyacetic acid,  
 3-[2-(1,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,  
 3-[2-(2,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,  
 3-(2-Diphenylmethoxyaminocarbonylethyl)phenoxyacetic acid,  
 10 3-[2-[(1,1-Diphenylmethylenediamino)aminocarbonyl]ethyl]phenoxyacetic acid,  
 3-(4-Diphenylaminosulfonyl-3-butenyl)phenoxyacetic acid,  
 3-(4-Diphenylaminosulfonylbutyl)phenoxyacetic acid,  
 15 4-(2-Benzoylaminoethyl)phenoxyacetic acid,  
 4-[2-(N,N-Diphenylaminocarbonylamino)ethyl]phenoxyacetic acid,  
 4-(2-(N,N-Diphenylaminomethylcarbonylamino)ethyl)phenoxyacetic acid.  
 4-(2-Phenylaminothiocarbonylaminoethyl)phenoxyacetic acid,  
 15 4-(2-Phenylsulfonylaminoethyl)phenoxyacetic acid,  
 4-[2-(N,N-Diphenylaminocarbonylaminoimino)ethyl]phenoxyacetic acid.  
 3-(3-Diphenylmethoxyaminosulfonylpropyl)phenoxyacetic acid.  
 3-[3-[(N,N-Diphenylamino)aminosulfonyl]propyl]phenoxyacetic acid,  
 20 3-[3-[(1,1-Diphenylmethylenediamino)aminosulfonyl]propyl]phenoxyacetic acid.  
 4-[2-[(N,N-Diphenylaminocarbonylamino)amino]ethyl]phenoxyacetic acid,  
 or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.

14. A compound according to claim 7, which is  
 3-(4-Diphenylmethoxybutyl)phenoxyacetic acid,  
 25 3-(3-Diphenylmethoxypropyl)phenoxyacetic acid,  
 3-(4-Triphenylmethoxybutyl)phenoxyacetic acid,  
 or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.
15. A compound according to claim 8, which is  
 30 3-(3-Diphenylmethoxycarbonylpropyl)phenoxyacetic acid,  
 or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine
16. A compound according to claim 9, which is  
 35 3-[3-(4-Diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid,  
 3-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,  
 2-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,  
 2-[5-(4-Diphenylmethylpyrazol-1-yl)pentyl]phenoxyacetic acid,  
 3-[2-(4-Diphenylmethylpyrazol-1-yl)ethyl]phenoxyacetic acid,  
 2-[3-(4-Diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid,  
 40 3-[3-(4-Diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,  
 4-[2-(4-Diphenylmethylpyrazol-1-yl)ethyl]phenoxyacetic acid,  
 4-[3-(4-Diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid,  
 4-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,  
 3-[(4-Diphenylmethylpyrazol-1-yl)methyl]phenoxyacetic acid,  
 45 2-[4-(4-Diphenylmethylpyrazol-1-yl)butyl]phenoxyacetic acid,  
 3-[3-[4-(1-Phenyl-1-(3-pyridyl)methyl)pyrazol-1-yl]-1-propenyl]phenoxyacetic acid,  
 2-Methoxy-5-[3(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid.  
 2-Nitro-5-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,  
 4-Nitro-3-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid.  
 50 2-Methyl-3-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,  
 2-Methyl-5-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,  
 3-Methyl-5-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,  
 4-Methyl-3-[3-(4-diphenylmethylpyrazol-1-yl)-1-propenyl]phenoxyacetic acid,  
 3-[2-(4-Diphenylmethylpyrazol-1-yl)ethoxy]phenoxyacetic acid,  
 55 3-[3-(2-Diphenylmethylimidazol-5-yl)propyl]phenoxyacetic acid,  
 3-[3-(3,4,5-Triphenylpyrazol-1-yl)propyl]phenoxyacetic acid,  
 3-[3-(4,5-Diphenylimidazolyl)propyl]phenoxyacetic acid,  
 3-[3-(4-Di(3-pyridyl)methylpyrazol-1-yl)propyl]phenoxyacetic acid,

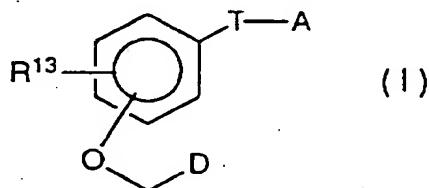
2-Methyl-3-[3-[4-[1-phenyl-1-(3-pyridyl)methyl]pyrazol-1-yl]propyl]phenoxy acetic acid,  
 3-[2-[4-[1-Phenyl-1-(3-pyridyl)methyl]pyrazol-1-yl]ethyl]phenoxyacetic acid, or its methyl ester, or its  
 octyl ester, or its acetamide, or its amide with glycine

- 5 17. A compound according to claim 10, which is  
   3-[3-(5-Diphenylmethylisoxazol-3-yl)propyl]phenoxyacetic acid,  
   3-[3-(3-Diphenylmethylisoxazol-5-yl)propyl]phenoxyacetic acid,  
   3-[3-(3-Diphenylmethylisothiazol-5-yl)propyl]phenoxyacetic acid,  
   3-[3-(3-Diphenylmethyl-1,2,4-oxadiazol-5-yl)propyl]phenoxyacetic acid,  
 10 3-[3-(5-Diphenylmethyl-1,2,4-oxadiazol-3-yl)propyl]phenoxyacetic acid.  
   3-[3-(Oxazol-2-yl)propyl]phenoxyacetic acid,  
   3-[3-(5-Ethyloxazol-4-yl)propyl]phenoxyacetic acid,  
   3-[3-[5-(3-pyridyl)methylisoxazol-3-yl]propyl]phenoxyacetic acid,  
 15 3-[3-[5-(1-Phenyl-1-(3-pyridyl)methyl)isoxazol-3-yl]propyl]phenoxyacetic acid,  
 or its methyl ester, or its octyl ester, or its acetamide, or its amide with glycine.

- 20 18. A compound according to claim 11, which is  
   3-[3-(4-Diphenylmethyl-1,2,3-triazol-2-yl)propyl]phenoxyacetic acid.  
   3-[3-(4-Diphenylmethyl-1,2,3-triazol-1-yl)propyl]phenoxyacetic acid.  
 25 3-[3-(4-Diphenylmethyl-1,2,3-triazol-3-yl)propyl]phenoxyacetic acid.  
 or its methyl ester, or its octyl ester, or its acetamide, or its amide with glycine.

19. A process for the preparation of phenoxyacetic acid derivatives of the formula (I):

25

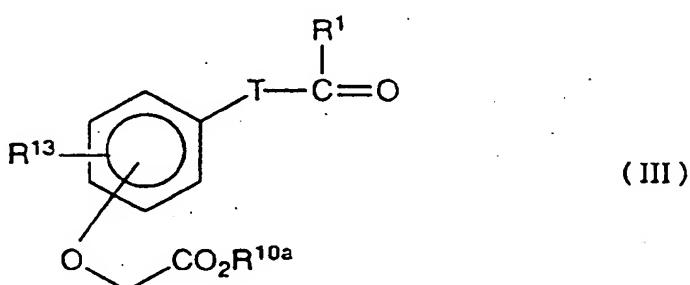


30

35 wherein all symbols are the meaning as hereinbefore defined in claim 1 or salts thereof or acid addition salts thereof, which is characterized by:

(i) the reaction of a compound of the formula (III):

40



45

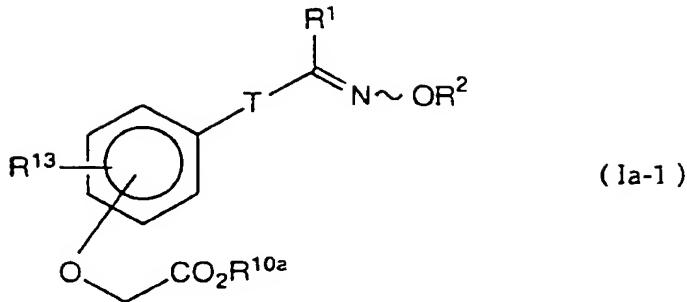
50 wherein R<sup>10a</sup> means methyl or ethyl and the other symbols are the same meaning as hereinbefore defined,  
 with a compound of the formula (a):

55

R<sup>2</sup>ONH<sub>2</sub>      (a)

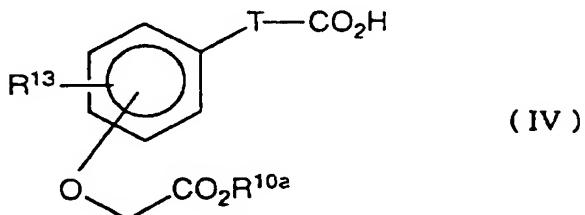
wherein R<sup>2</sup> is the same meaning as hereinbefore defined,

(ii) subjecting a compound obtained by reaction (i) of the formula (Ia-1):



wherein all the symbols are the same meaning as hereinbefore defined, to reduction.

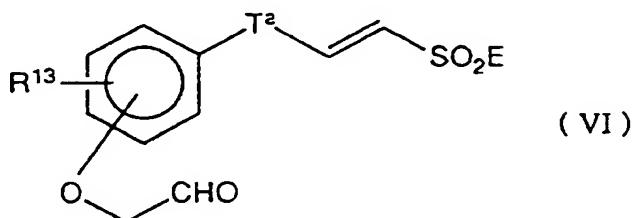
(iii) the amidation of a compound of the formula (IV):



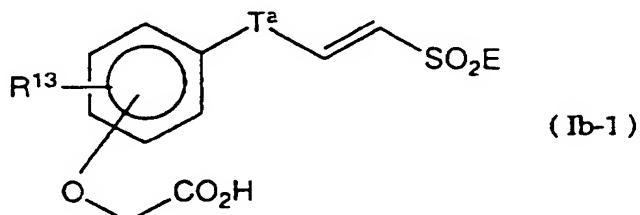
wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (b)

30 H E (b)

wherein E is the same meaning as hereinbefore defined.  
(iv) subjecting a compound of the formula (VI).



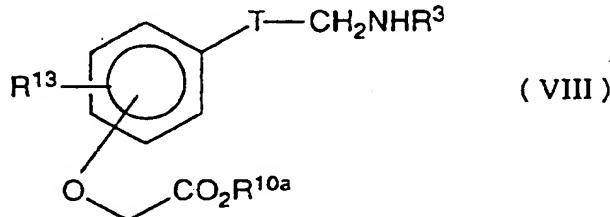
45 wherein T<sup>a</sup> is single bond, C1-4 alkylene, C2-4 alkenylene, or -O-(CH<sub>2</sub>)<sub>t</sub>-wherein t is 0-2, and the other symbols are the same meaning as hereinbefore defined, to Jone's oxidation,  
(v) subjecting a compound obtained by reaction (iv) of the formula (Ib-1).



wherein all the symbols are the same meaning as hereinbefore defined, to hydrogenation (including a series of reactions subjecting a compound of the formula (Ib-1) to methylesterification, and to hydrogenation, followed by hydrolysis of the ester bond, for the convenience of purification).

(vi) the amidation or thioamidation of a compound of the formula (VIII):

5



10

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (c)

20

$R^6CO_2H$  (c)  
wherein  $R^6$  is the same meaning as hereinbefore defined, or with a compound of the formula (d).

$R^4R^5N-L-CO_2H$  (d)

25

wherein all the symbols are the same meaning as herein before defined, or with a compound of the formula (e)

$R^4-N=C=S$  (e)

30

wherein  $R^4$  is the same meaning as hereinbefore defined, or with a compound of the formula (f):

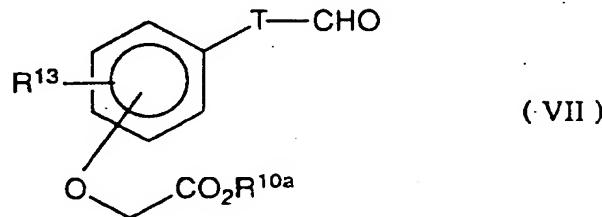
$R^6SO_2Cl$  (f)

wherein  $R^6$  is the same meaning as hereinbefore defined,

35

(vii) the reaction of a compound of the formula (VII):

40



45

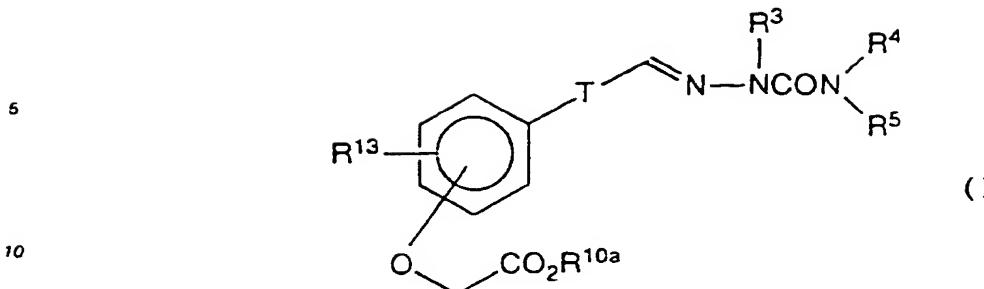
wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (g):

50

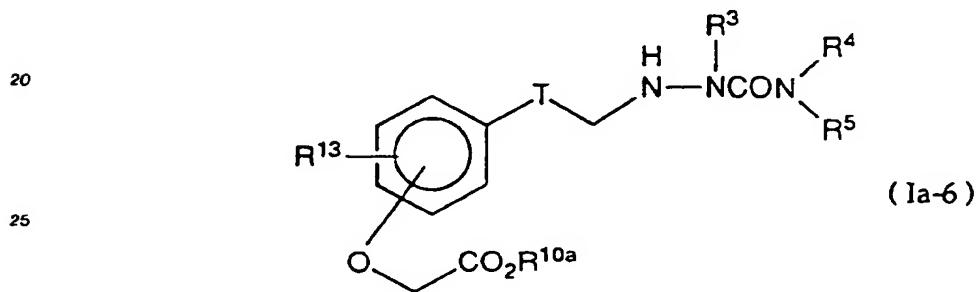
$H_2N-NR^3-CONR^4R^5$  (g)

wherein all the symbols are the same meaning as hereinbefore defined.  
(viii) subjecting a compound obtained by reaction (vii) of the formula (Ia-5)

55



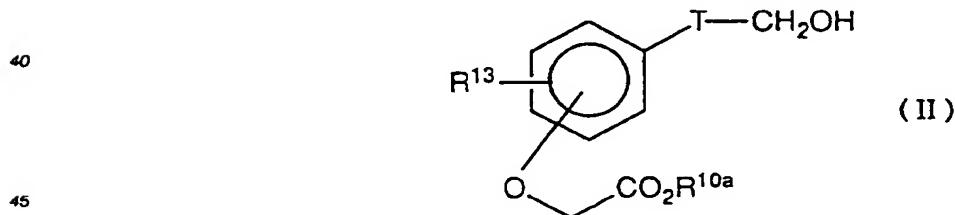
15 wherein all the symbols are the same meaning as hereinbefore defined, to reduction,  
(ix) the reaction of a compound obtained by reaction (viii) of the formula (Ia-6)



30 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (h):

R<sup>3a</sup>I (h)

35 wherein R<sup>3a</sup> is C1-6 alkyl or phenyl,  
(x) the reaction of a compound of the formula (II):



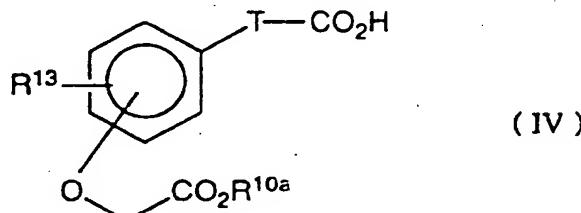
50 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (i).



wherein R<sup>6</sup> is the same meaning as hereinbefore defined, or with a compound of the formula (s).

R<sup>6</sup>X (s)

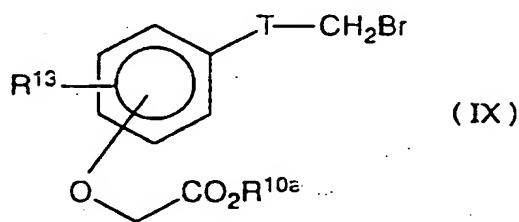
wherein X is halogen and R<sup>6</sup> is the same meaning as hereinbefore defined,  
 5 (xi) the esterification of a compound of the formula (IV)



wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (j):

R<sup>6</sup>OH (j)

wherein R<sup>6</sup> is the same meaning as hereinbefore defined.  
 (xii) the reaction of a compound of the formula (IX)



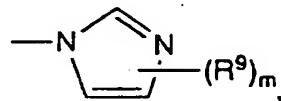
35 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (k):

G H (k)

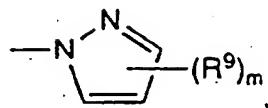
wherein

G is

i)

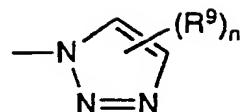


50 ii)



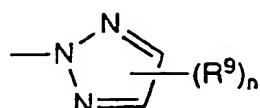
55

iii)



or

iv)



15

wherein all the symbols are the same meaning as hereinbefore defined, or with a compound of the formula (q):



20

wherein all the symbols are the same meaning as hereinbefore defined, or with a compound of the formula (r):

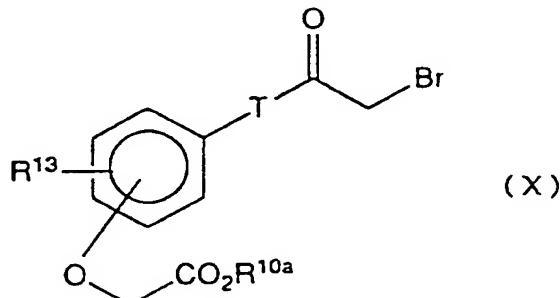


25

wherein all the symbols are the same meaning as hereinbefore defined

(xiii) the reaction of a compound of the formula (x):

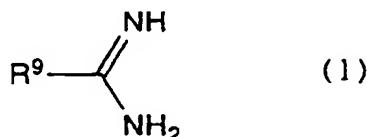
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35

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (l):

45

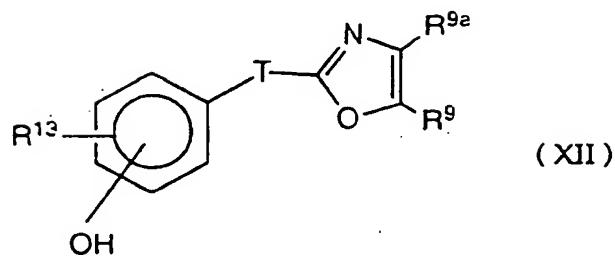


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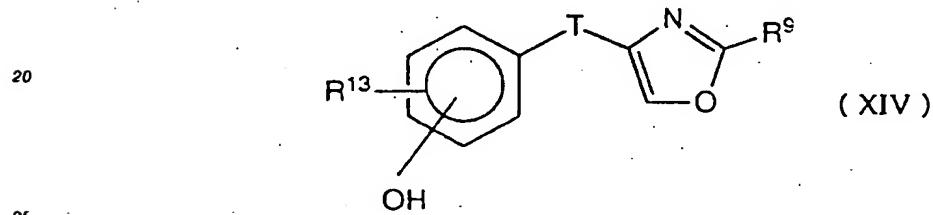
wherein R<sup>9</sup> is the same meaning as hereinbefore defined,

(xiv) the reaction of a compound of the formula (XII):

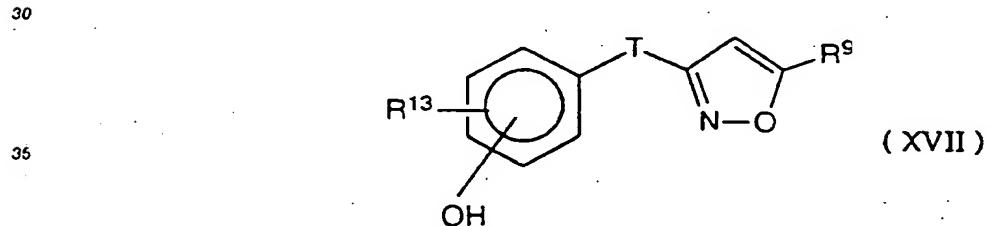
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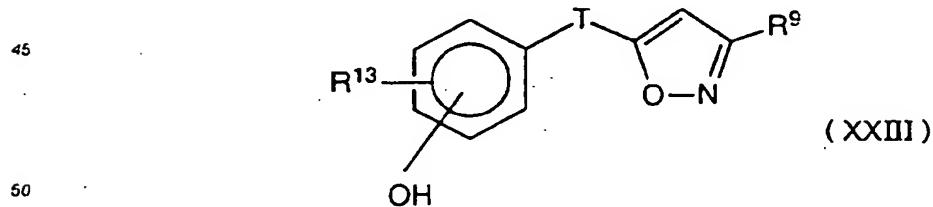
wherein R<sup>9a</sup> is phenyl, C1-4 alkyl or C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen and the other symbols are the same meaning as hereinbefore defined, or  
15 a compound of the formula (XIV).



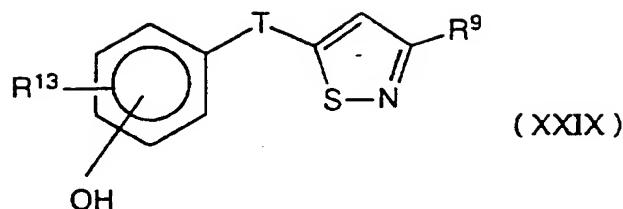
wherein all the symbols are the same meaning as hereinbefore defined, or a compound of the formula (XVII):



40 wherein all the symbols are the same meaning as hereinbefore defined, or a compound of the formula (XXIII):



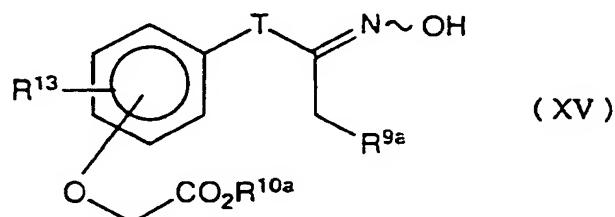
55 wherein all the symbols are the same meaning as hereinbefore defined, or a compound of the formula (XXIX)



10 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (m):



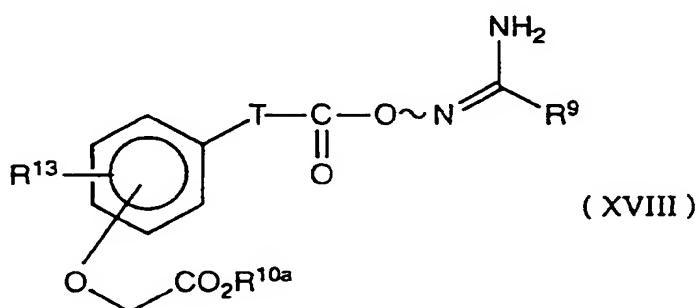
wherein  $\text{R}^{10a}$  is the same meaning as hereinbefore defined,  
(xv) the reaction of a compound of the formula (XV)



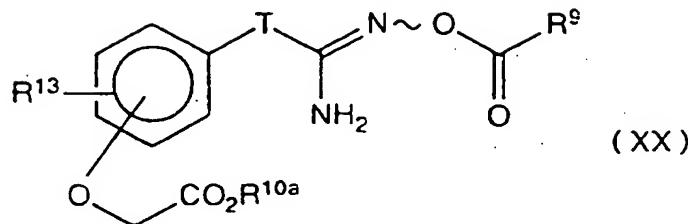
30 wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (n):



wherein  $\text{R}^9$  is the same meaning as hereinbefore defined,  
(xvi) the cyclization of a compound of the formula (XVIII)



50 wherein all the symbols are the same meaning as hereinbefore defined,  
(xvii) the cyclization of a compound of the formula (XX)

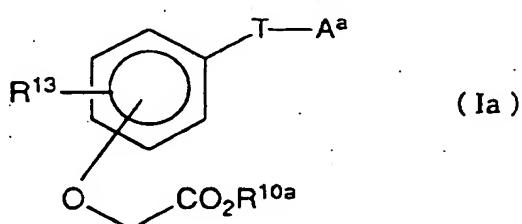


10

wherein all the symbols are the same meaning as hereinbefore defined.

(xviii) the hydrolysis of a compound obtained by hereinbefore reaction (i), (ii), (iii), (vi), (vii), (viii), (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xvi) or (xvii) of the formula (Ia):

15



20

25 wherein

Aa is

- i) -CR<sup>1</sup>=N-OR<sup>2</sup>,
- ii) -CHR<sup>1</sup>-NH-OR<sup>2</sup>,
- iii) -COE,
- iv) -CH<sub>2</sub>NR<sup>3</sup>-Y,
- v) -CH=N-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- vi) -CH<sub>2</sub>-NH-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- vii) -CH<sub>2</sub>-NR<sup>3</sup>-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>,
- viii) -CH<sub>2</sub>OR<sup>6</sup>,
- ix) -CO<sub>2</sub>R<sup>6</sup>,
- x) -CH<sub>2</sub>G,
- xi) -CH<sub>2</sub>-O-N=CR<sup>7</sup>R<sup>8</sup>,
- xii) -CH<sub>2</sub>-O-NHCHR<sup>7</sup>R<sup>8</sup>,
- xiii)

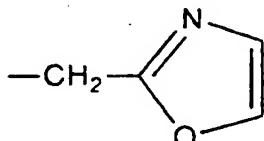
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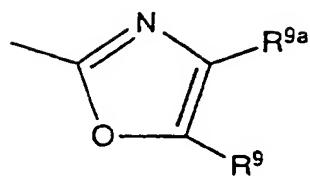
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xiv)

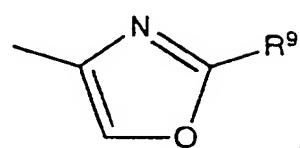


EP 0 558 062 A2

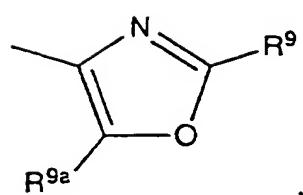
xv)



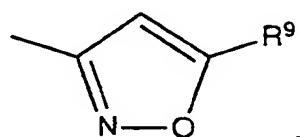
xvi)



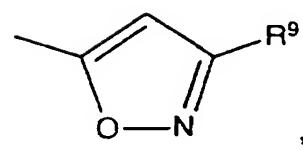
xvii)



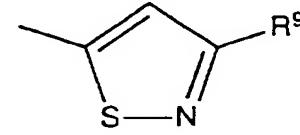
xviii)



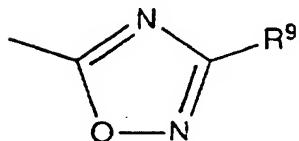
xix)



xx)



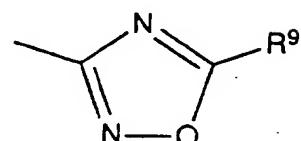
xxi)



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or

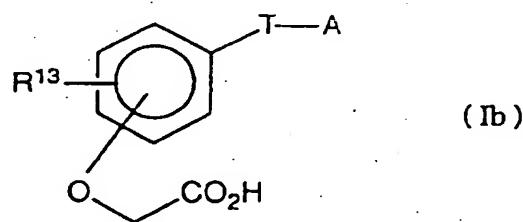
xxii)



20

and the other symbols are the same meaning as hereinbefore defined,  
 (xix) the esterification of a compound obtained by hereinbefore reaction (iv), (v) or (xviii) of the formula (Ib):

25



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wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (o):

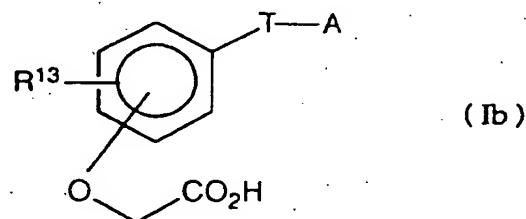
R<sup>10b</sup>OH (o)

40

wherein R<sup>10b</sup> is C1-12 alkyl,

(xx) the amidation of a compound obtained hereinbefore reaction (iv), (v), or (xviii) of the formula (Ib):

45



50

wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (p):

55

R<sup>11</sup>R<sup>12</sup>NH (p)

wherein all the symbols are the same meaning as hereinbefore defined, or

EP 0 558 062 A2

(xxi) the conversion of a phenoxyacetic acid of the formula (I) into the corresponding salt or acid addition salt thereof by known method, if desired.

20. A pharmaceutical composition which comprises, as active ingredient, an effective amount of a phenoxyacetic acid derivative of the formula (I) depicted in claim 1 or a non-toxic salt thereof, or a non-toxic acid addition salt thereof, with a pharmaceutical carrier or coating.

21. For use in the prevention and/or the treatment of thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer or hypertension, which comprises the administration of an effective amount of a phenoxyacetic acid derivative of the formula (I) depicted in claim 1 or a non-toxic salt thereof, or a non-toxic acid addition salt thereof.

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(19) Europäisches Patentamt  
 European Patent Office  
 Office européen des brevets



(11) Publication number:

0 558 062 A3

(12)

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 C07D 263/32, C07D 275/02,  
 C07D 261/08, A61K 31/19,  
 A61K 31/395, A61K 31/21,  
 C07C 251/40, C07C 239/20,  
 C07C 235/38, C07C 235/34,  
 C07C 243/32, C07C 311/27,  
 C07C 59/70

(22) Date of filing: 26.02.93

(30) Priority: 28.02.92 JP 78330/92

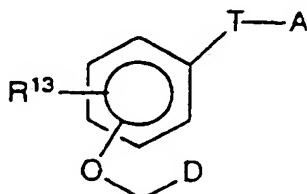
Minase Res. Institute,  
 3-1-1 Sakurai Shimamoto-cho  
 Mishima-gun, Osaka(JP)(43) Date of publication of application  
 01.09.93 Bulletin 93/35Inventor: Takahashi, Kanji, c/o Ono  
 Pharmacuetical Co., Ltd.(64) Designated Contracting States:  
 AT BE CH DE DK ES FR GB GR IE IT LI LU MC  
 NL PT SEMinase Res. Institute,  
 3-1-1 Sakurai Shimamoto-cho  
 Mishima-gun, Osaka(JP)(66) Date of deferred publication of the search report  
 12.01.94 Bulletin 94/02Inventor: Tokumoto, Hidekado, c/o Ono  
 Pharmacuetical Co. Ltd(71) Applicant: ONO PHARMACEUTICAL CO., LTD.  
 1-5, Doshomachi 2-chome  
 Chuo-ku  
 Osaka-shi Osaka(JP)Minase Res. Institute,  
 3-1-1 Sakurai Shimamoto-cho  
 Mishima-gun, Osaka(JP)(72) Inventor: Hamanaka, Nobuyuki, c/o Ono  
 Pharmacuetical Co. Ltd(74) Representative: Henkel, Feiler, Hänel &  
 Partner  
 Möhlstrasse 37  
 D-81675 München (DE)

(54) Phenoxyacetic acid derivatives and pharmaceutical compositions containing them.

(55) We proposed a novel compound having an activity of PGI<sub>2</sub> receptor agonist  
 A phenoxyacetic acid derivative of the formula

A is -C(R<sup>1</sup>)=N-OR<sup>2</sup>, -CH(R)NH-OR<sup>2</sup>, -COE,  
 -SO<sub>2</sub>E, -CH<sub>2</sub>-NR<sup>3</sup>-Y, -Z-NR<sup>3</sup>-CONR<sup>4</sup>R<sup>5</sup>, -CH<sub>2</sub>-OR<sup>6</sup>,  
 -CO<sub>2</sub>R<sup>6</sup>, -CH<sub>2</sub>-O-N=CR<sup>7</sup>R<sup>8</sup>, -CH<sub>2</sub>-O-NHCHR<sup>7</sup>R<sup>8</sup>,  
 substituted by imidazolyl(methyl), pyrazolylmethyl,  
 oxazolyl(methyl), thioxazolyl, isoxazolyl, isothiazolyl,  
 oxadiazolyl, triazolylmethyl;  
 T is alkylene, alkenylene, etc.;  
 D is -CO<sub>2</sub>R<sup>10</sup>, -CONR<sup>11</sup>R<sup>12</sup>;

E is (substitution) amino, hydrazino;  
 Y is substituted (thio) carbonyl, substituted sulfonyl,  
 Z is -CH=N-, -CH<sub>2</sub>NR<sup>3</sup>-,  
 R<sup>1</sup>, R<sup>3</sup>, R<sup>10</sup>-R<sup>13</sup> is each H or alkyl, etc.;



**EP 0 558 062 A3**

R<sup>2</sup>, R<sup>4</sup>-R<sup>5</sup> is each H, alkyl or alkyl substituted by phenyl or hetero ring, etc. and non-toxic salts thereof, non-toxic acid addition salts thereof, possess an agonistic on PGI<sub>2</sub> receptor, so it is useful for prevention and/or treatment of thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer and hypertension.



European Patent  
Office

## PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

EP 93 10 3113 +2

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X	GB-A-1 079 414 (T.J. SMITH & NEPHEW LTD) * claims; examples *	1,2,6, 20	C 07 D 231/12 C 07 D 249/04 C 07 D 401/06 C 07 D 213/53 C 07 D 263/32 C 07 D 275/02 C 07 D 261/08 A 61 K 31/19 A 61 K 31/395 A 61 K 31/21 C 07 C 251/40
X	FR-A-2 434 155 (KISSEI PHARMACEUTICAL CO., LTD AND ONO PHARMACEUTICAL CO., LTD) * page 21; example 6; page 29 *	1,2,9, 19-21	
X	EP-A-0 300 454 (HODOGAYA CHEMICAL CO., LTD) * page 3 - page 8 *	1-4,19	
X	DE-A-2 432 560 (BOEHRINGER MANNHEIM GMBH.) * claims; examples *	1-3,19, 20	
X	EP-A-0 442 448 (BRISTOL-MYERS SQUIBB COMP.) * page 16 - page 17; page 26; page 35 - page 38 *	1-3,9, 19-21 -/-	
TECHNICAL FIELDS SEARCHED (Int. Cl. 5)			
C 07 D C 07 C			
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely:</p> <p>Claims searched incompletely:</p> <p>Claims not searched:</p> <p>Reason for the limitation of the search.</p>			
see sheet -C-			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	29-09-1993	PAUWELS G R A	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



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### PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 93 10 3113

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	US-A-5 021 415 (BRISTOL-MYERS SQUIBE COMP.) * examples 5,6 * -----	1,20,21	



EP 93 10 3113 -C-

INCOMPLETE SEARCH

Claims searched completely : 1-20  
Claims searched incompletely : 21

Remark : Although claim 21 is directed to a method of treatment of (diagnostic method practised on) the human/animal body (Article 52(4) EPC) the search has been carried out and based on the alleged effects of the compound/composition.

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